LEVEL 1 - 1 OF 3 PATENTS

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Polycyclic quinoline, naphthyridine and pyrazinopyridine derivatives

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REF-CITED:

U.S. PATENT DOCUMENTS

3,931,199	1/1976	* Nakanishi et al.	546#83
3,931,205	1/1976	* Nakanishi et al.	546#83
3,947,449	3/1976	* Durchkheimer et al.	546#103
4,596,809	6/1986	* Sherlock	546#84
4,680,297	7/1987	* Blythin et al.	514#293
4,680,298	7/1987	* Blythin	514#293
4,687,774	8/1987	* Smith et al.	514#293
4,760,073	7/1988	* Blythin et al.	514#293
4,801,589	1/1989	* Smith et al.	514#291
4,882,332	11/1989	* Siegel et al.	514#255

FOREIGN PATENT DOCUMENTS

0127135	12/1984	* European Patent Organization	546#84
1585099	1/1970	* France	546#83

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OTHER PUBLICATIONS

Chem. Ab. vol. 96: No. 217821K.
Chem. Ab. vol. 85, No. 108567: p. 455 (1976).
Chemical Abstracts. vol. 101, Abstract No. 38382t, 1984.
Chem. Abstracts, 91(5): 32785e (1979) p. 33.
Chem. Abstracts, 88(13): 89668m (1978) p. 522.
Chem. Abstracts, (85)3: 21376x (1976) p. 695.
Chem. Abstracts, 74(15): 74797q (1971) p. 303.
Chem. Abstracts, 85(7): 46621m (1976) p. 536.
Chem. Abstracts, 90(25): 203821z (1979) pp. 600-601.
Chem. Abstracts, 93(5): 46364v (1980) p. 902.
Chem. Abstracts, 95(13): 115339w (1981) p. 686.
Chem. Abstracts, 80(19): 108503g (1974) p. 419.
Chem. Abstracts, 82(1): 4230r (1976) pp. 367-368.

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ABST:
Novel polycyclic quinoline, naphthyridine and pyrazinopyridine derivatives are disclosed which are useful for treating allergic reactions, inflammation, peptic ulcers, hypertension, and hyperproliferative skin diseases and for suppressing the immune response in mammals. Methods for preparing said compounds are also disclosed.

NO-OF-CLAIMS: 8

EXMPL-CLAIM: <=11> 1

NO-OF-FIGURES: 0

NO-DRWNG-PP: 0

PARCASE:

This is a division of U.S. application Ser. No. 307,646 filed Feb. 7, 1989 now U.S. Pat. No. *4,988,705*, which is a division of U.S. application Ser. No. 017,027, filed Feb. 17, 1987 (now U.S. Pat. No. *4,810,708*), which is a continuation-in-part of U.S. application Ser. No. 861,788, filed May 15, 1986 (now abandoned), which in turn is a continuation-in-part of U.S. application Ser. No. 744,865, filed Jun. 13, 1985 (now abandoned).

SUM:

BACKGROUND OF THE INVENTION

The present invention relates to novel polycyclic compounds which are useful

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in the treatment of allergic diseases, inflammation, peptic ulcers, hypertension, hyperproliferative skin diseases and in suppressing the immune response.

SUMMARY OF THE INVENTION

The invention in its chemical compound aspect involves a compound having the structural formula I [See Original Patent for Chemical Structure Diagram] I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

in formula I:

the dotted lines (---) represent optional double bonds;

W is [See Original Patent for Chemical Structure Diagram] II [See Original Patent for Chemical Structure Diagram] III [See Original Patent for Chemical Structure Diagram] IV [See Original Patent for Chemical Structure Diagram] V [See Original Patent for Chemical Structure Diagram] VI [See Original Patent for Chemical Structure Diagram] VII

T and V may be the same or different and each represents H, OH, alkyl, alkoxy, phenyl, or substituted phenyl;

in addition, T may also be F, Cl, or Br;

X and M may be the same or different and each independently represents -CH(R<a>)- or -NA- when the dotted line attached thereto does not represent a double bond; or X and M each independently represents =CH- or =N- when the dotted line attached thereto represents a double bond; or when M is N and the dotted lines in ring t both represent double bonds, X and T together with the carbon atom of the ring t therebetween may also represent a group [See Original Patent for Chemical Structure Diagram]

wherein X is a carbon atom and Q0-3 represents zero, 1, 2 or 3 Q substituents as defined below;

each A is independently selected from H, alkyl, CH2CH2OH, COR<b> , COOR<e> , SO2R<b > or (CH2) s R<c> ;

Z is O, S, N-R<e > or N(OR<i>);

B is alkyl, alkenyl [provided k is not zero], NH2, COOR<e> , O(CO)R<e> , or an aryl group selected from phenyl, naphthyl, indenyl, indanyl, phenanthridinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, furanyl, thienyl, benzofuranyl, indolyl, imidazolyl, pyrazolyl, triazolyl, or thiazolyl any of which aryl groups may be substituted with up to three of any of the following substituents, Q: halogen, hydroxy, nitro, alkyl, CH2OH, trifluoromethyl, cyano, N(R<f>)2, cycloalkyl, alkoxy, alkenyloxy, alkynyloxy, S(O) r R<e> , NHSO2R<e> , NHSO2CF3, NHCOCF3, SO2NH2, SO2NHR<e> , SO2N(R e

)2COR<h> , O-D-COR<h> , or NHCOR<d> ;

R<a > is H, OH, alkyl, phenyl, substituted phenyl, phenylalkyl or substituted phenylalkyl;

R<b > is H, alkyl, phenyl, substituted phenyl, or N(R<e>)2;

R<c > represents carboxyl or N(R<i>)2;

R<d > represents H, alkyl, alkoxy, COR<j> , or NHR<k> ;

each R<e > independently represents alkyl, phenyl, substituted phenyl, benzyl or substituted benzyl;

each R<f > independently represents H or alkyl;

R<h > represents OH, NH2 or OR<e> ;

each R<i > independently represents H or alkyl;

R<j > represents OH or alkoxy;

R<k > represents H or alkyl;

D represents alkylene;

k is 0, 1 or 2;

r is 0, 1 or 2; and

s is 1, 2, 3, 4 or 5;

in formula II:

the dotted line represents an optional double bond;

Y and Y' are both H or, when represents a double bond, Y and Y' together with the carbon atoms to which they are attached may also represent a phenyl ring which may be substituted with up to 3 substituents independently selected from hydroxy, alkoxy, alkyl or halo; and

m and n may be the same or different and are 0, 1, 2, 3 or 4, provided that the sum of m and n is 1, 2, 3 or 4;

in formula III:

the dotted line represents one optional double bond or two optional non-cumulated double bonds;

one of a, b, and c is N (if the dotted line attached thereto represents a double bond), N< + > O< - > (if the dotted line attached thereto represents a double bond), O, S(O) r , N-R<m> , or N-CO-R<n> , or d is N (if the dotted line attached thereto represents a double bond), -NR<m> , or N-CO-R<n> , and each of the other three may be the same or different and each represents CH2 or CH (if the dotted line attached thereto represents a double bond);

r is as defined above;

R<m > represents H, alkyl, acyl, benzyl or substituted benzyl; and

R<n > represents phenyl, substituted phenyl, alkoxy, phenoxy, substituted phenoxy, phenylalkoxy, or substituted phenylalkoxy;

in formula IV:

R<1 > and R<2 > may be the same or different and each is selected from H (provided both are not H), alkyl, phenyl, substituted phenyl, hydroxy, COOR<e> , O(CO)R<e> , cyano, carboxyl, CONH2, CON(R<e>)2, CONHR<e> , or OR<e> ; or R<1 > and R<2 > are attached to the same carbon atom of the ring [See Original Patent for Chemical Structure Diagram]

and together represent a carbonyl oxygen or a ketal thereof selected from [See Original Patent for Chemical Structure Diagram]

or R<1 > and R<2 > together with two adjacent carbon atoms of the [See Original Patent for Chemical Structure Diagram]

ring represent an epoxide, aziridine, furane, thiophene, pyrrole, N-alkylpyrrole, isopyrrole, 3-isopyrrole, pyrrolidine, triazole, triazolidine, isoxazole, isothiazole, isoxazolidine, isoxazoline, pyrazole, N-alkylpyrazole, pyrazoline, or pyrazolidine ring;

R<w > and R<y > may be the same or different and each represents alkyl; and

R<e > is as defined above;

in formula V:

R<3> , R<4> , R<5 > and R<6 > may be the same or different and are hydrogen or alkyl; and

q is 1 or 2;

in formula VI:

the dotted line represents an optional double bond between e and f or between f and g as defined below:

e, f and g are defined as follows:

(i) e represents O, S(O) r , N-R<m > or N-COR<n> , and f and g both represent CR<p > (if the dotted line between f and g represents a double bond) or CHR<p> ; or

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(ii) f represents O, S(O) r , N-R<m > or N-COR<n> , and e and g both represent CHR<p> ; or

(iii) g represents N (if the dotted line between f and g represents a double bond), f represents CR<p> , and e represents CHR<p> ; or
(iv) g represents N-R<m > or N-COR<n> , and e and f both represent CR<p > (if the dotted line between e and f represents a double bond) or both represent CHR<p> ;

each R<p > is independently selected from H, alkyl, acyl or COOR<f> ; and

R<f> , R<m> , R<n > and r are as defined above; and

in formula VII:

one of J and L is CHR<q > and the other is CR<r> R<s > or, when represents a double bond between J and L, one of J and L is CR<q > and the other is CR<r> ;

R<q > represents H, COOR<t> , or alkyl;

R<r > and R<s > may be the same of different and each is selected from H, alkyl, acyl, -COOR<e> , O(CO)R<e> , -CN, phenyl sulfonyl, substituted phenyl sulfonyl, alkyl sulfonyl, nitro; or R<q > and R<r > together with the carbon atoms to which they are attached represent a carbocyclic ring having from 5 to 8 carbon atoms optionally containing one carbon-carbon double bond or represent a heterocyclic ring selected from [See Original Patent for Chemical Structure Diagram]

R<e > is as defined above; and

R<t > represents H, alkyl, phenyl, substituted phenyl, benzyl or substituted benzyl.

In formula I, k is preferably zero, the dotted lines in ring t preferably represent double bonds and M is preferably N. T and V are preferably H, Z is preferably O, and X is preferably CH. B in formula I is preferably phenyl or phenyl substituted with up to 3 Q substituents as defined above. Substituent Q is preferably present in the 2-, 3- or 4-; 2- and 3-; 2- and 4-; 2- and 5-; 3- and 4-; or 3- and 5-positions.

A preferred subgenus of formula II has structural formula [See Original Patent for Chemical Structure Diagram] IIa

wherein B, m, and n are as defined above.

A second preferred subgenus of formula II has structural formula [See Original Patent for Chemical Structure Diagram] IIb

wherein Q0-3 represents up to three Q substituents as defined above. Q preferably represents a 3-Cl, 3-CH3S or 3-NO2 substituent in such formula.

A third preferred subgenus of formula II has structural formula [See Original Patent for Chemical Structure Diagram] IIc

wherein Q0-3 represents up to three Q substituents as defined above. Q preferably is absent or represents a 3-CF3, 3-S-CH3, 4-CH3 or 3-NO2 phenyl substituent in a such formula.

In formula III, a, c and d preferably are CH2, the dotted lines preferably do not represent double bonds, and b preferably represents O, S(O) r , N-R<m > or N-CO-R<n > wherein r, R<m > and R<n > are as defined above. More preferably, b is N-R<m > and R<m > is acyl, e.g., acetyl.

A preferred subgenus of formula III has structural formula [See Original Patent for Chemical Structure Diagram] IIIa

wherein the dotted lines represent optional double bonds; Q0-3 represents up to three Q substituents as defined above; and E represents N< + > -O< - > when the dotted line attached to E represents a double bond or E represents N-R<m > or N-CO-R<n > (wherein R<m > and R<n > are as defined above) when the double bond represented by the dotted line attached to E is absent.

A preferred subgenus of the compounds having ring W represented by formula is represented by the formula [See Original Patent for Chemical Structure Diagram] IVa

wherein B and R<1 > are as defined above. In such formula IVa, R<1 > is preferably COOR<e > wherein R<e > is as defined above, R<e > preferably being C2H5 and B preferably being 3-chlorophenyl. Alternatively, R<1 > in formula IVa is preferably CH3 and B preferably represents 3-chlorphenyl, 3-methoxyphenyl, 3-methylthiophenyl or 3-nitrophenyl group.

In formula VI, e and f preferably represent CH2 and the dotted lines do not represent double bonds, with g being defined as above. The letter g preferably represents N-R<m> , more preferably N-CH3 while B preferably represents phenyl or substituted phenyl such as 3-trifluoromethylphenyl.

In formula VII, the dotted line preferably does not represent a double bond and J and L together preferably represent a heterocyclic ring [See Original Patent for Chemical Structure Diagram]

wherein R<t > is phenyl. Alternatively, the dotted line preferably does not represent a double bond and J and L both preferably represent CHCOOCH3.

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Preferred compounds of the invention include [See Original Patent for Chemical Structure Diagram] and [See Original Patent for Chemical Structure Diagram]

or a pharmaceutically acceptable salt thereof. Compound A is particularly useful in the treatment of allergic reactions, while Compounds B, C and D are particularly useful in the treatment of inflammation.

When utilized herein, the terms below have the following scope:

halo-represents fluoro, chloro, bromo and iodo;

alkyl (including the alkyl portion of alkoxy, phenylalkyl, phenylalkoxy and alkylsulfonyl) and alkylene-represent straight and branched carbon chains and contain from 1 to 6 carbon atoms;

alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and contain from 2 to 6 carbon atoms;

alkenyloxy and alkynyloxy-represents straight and branched carbon chains having at least one carbon-to-carbon double or triple bond, respectively, and contains from 3 to 6 carbon atoms, with the proviso that the oxygen atom is not bound to an olefinic or acetylenic carbon atom thereof;

cycloalkyl-represents saturated carbocyclic rings having from 5 to 8 carbon atoms;

substituted phenyl, substituted phenylalkyl, substituted phenoxy, substituted phenylalkoxy, and substituted benzyl-represents phenyl, phenylalkyl, phenoxy, phenylalkoxy and benzyl groups wherein the phenyl ring thereof is substituted with up to 3 substituents Q as defined above, with the Q substituents being the same or different when there are 2 or 3 Q substituents; and

acyl-represents a group alkyl-CO- wherein alkyl is as defined above.

The invention also involves a pharmaceutical composition which comprises a compound having structural formula I in combination with a pharmaceutically acceptable carrier.

The invention further involves methods for treating allergic reactions, inflammation, peptic ulcers, hypertension and hyperproliferative skin diseases (e.g., psoriasis, lichenified eczema or seborrheic dermatitis) and for suppressing the immune response in a mammal which comprises administering the above defined pharmaceutical composition to said mammal in an amount effective to achieve such purposes.

DESCRIPTION OF THE INVENTION

The group B in formula I may represent various aromatic and heterocyclic rings. These rings may be attached to the group -(CH2) k - (or to the N atom of the middle ring of structural formula I if k is zero) via any of the available substitutable atoms of such B aromatic or heterocyclic aromatic ring. Examples of suitable aryl heterocyclic groups B include 2-, 3- or 4-pyridinyl, 2- or 3-furanyl, 2- or 3-thienyl, 2, 4- or 5-thiazolyl, 2-, 4- or 5-imidazolyl, 2-,

4-, 5- or 6-pyrimidinyl, 2- or 3-pyrazinyl, 3- or 4-pyridazinyl, 3-, 5- or 6-[1,2,4-triazinyl], 2-, 3-, 4-, 5-, 6- or 7-benzofuranyl, 2-, 3-, 4-, 5-, 6- or 7-indolyl, or 3, 4- or 5-pyrazolyl.

Also, in formula IV, when R<1 > and R<2 > together represents a heterocyclic ring system, all possible orientations of the heteroatoms in such rings are intended. For example, R<1 > and R<2 > together with the adjacent carbon atoms of the ring [See Original Patent for Chemical Structure Diagram]

to which they are attached may form a furanyl ring with the oxygen atom thereof in any possible position in the furanyl ring.

As noted above, the compounds of the invention may include up to three Q substituents on an aromatic "B" group depending upon the available sites for substitution. In compounds where there is more than one such Q substituent, they may be the same or different. Thus, compounds having combinations of different Q substituents are contemplated within the scope of the invention. Examples of suitable Q substituents include hydroxy, methyl, chloro, bromo, nitro, cyclohexyl, allyloxy, 2-propynyloxy, methylthio, methylsulfonyl, carboxy, acetoxymethoxy, acetylamino, methylsulfonylamino and the like.

Where two substituents appear on the same group, e.g. R<e > in SO2N(R<e>)2 or R<f > in N(R<f>)2, such substituents may be the same or different. The same is true when a particular substituent (such as R<e>) appears in two or more positions in a compound of formula I. For example, when in formula I, Z is NR<e> , ring W is formula II, and R<1 > represents COOR<e> , the R<e > groups may be the same or different.

Certain compounds of the invention may exist in isomeric forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures.

The compounds of the invention of formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemihydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

Certain compounds of the invention will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain compounds of the invention also form pharmaceutically acceptable salts, e.g., acid addition salt and quaternary ammonium salts. For example, the pyrido- or pyrazino- nitrogen atoms may form salts with strong acid, while compounds having basic Q substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicyclic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and

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carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The quaternary ammonium salts are prepared by conventional methods, e.g., by reaction of a tertiary amino group in a compound of formula I with a quaternizing compound such as an alkyl iodide, etc. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

The compounds of the invention which possess an aromatic ring nitrogen atom, as defined above, may also form quaternary salts at an aromatic ring nitrogen atom.

All such acid, base and quaternary salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

The following processes A. to D. may be employed to produce various compounds in accordance with formula I. Processes A. to C. produce compounds of formula I where ring W is in accordance with formulas II, III, IV, V and VI, Z is O, and the dotted lines in ring t represent double bonds:

A. A compound of formula X [See Original Patent for Chemical Structure Diagram] X

is reacted with a compound of formula XI [See Original Patent for Chemical Structure Diagram] XI

wherein M, T, V, X, k, and B are as previously defined, ring W is in accordance with formulas II to VI, and L<1 > is a leaving group to produce a compound of formula I, a compound of formula Ia, [See Original Patent for Chemical Structure Diagram] Ia

or a mixture of compounds of formulas I and Ia, and if only a compound of formula Ia is produced, followed by converting the compound of formula Ia to a compound of formula I by treatment of the compound of formula Ia with strong acid; or if a mixture of compounds of formulas I and Ia was produced, optionally followed by treatment of the mixture with strong acid to convert the compound of formula Ia to a compound of formula I.

The starting materials having structural formula X and XI are known in the art. L<1 > can be, for example, phenoxy, alkoxy, phenylalkoxy, etc. Compounds in accordance with formula X having -OH in the position of L<1 > can be converted to compounds wherein L<1 > is phenoxy, alkoxy or phenylalkoxy, by standard

methods. Compounds of formula X wherein X and M are N, i.e., 2-substituted amino-3-pyrazine carboxylate esters may be prepared by known methods. For example, 2-phenylamino-3-pyrazine carboxylic acid is known from C.A., 75 20154e (1971).

The ketones XI, may be prepared by standard procedures or by obvious variations thereof. Other ketones having structural formula XI such as cyclopentanone, cyclohexanone and the like are available commercially.

The reaction of the compounds of formulas X and XI may be carried out by contacting X and XI in a non-reactive solvent in the presence of a basic reagent, preferably at an elevated temperature for a sufficient amount of time until the reaction is substantially completed. The progress of the reaction may be monitored by thin layer chromatography, if desired. Suitable non-reactive solvents for purposes of the reaction are tetrahydrofuran, toluene, dimethylsulfoxide, N,N-dimethylformamide and the like. Suitable basic reagents are lithium bistrimethylsilylamide, sodium amide and the like. Other suitable basic reagents and solvents will suggest themselves to those skilled in the art.

The reaction of X and XI may yield compounds of formula I, compounds of formula Ia, or a mixture of the two. If only a compound of formula Ia is formed, it may be converted to a compound of formula I by treatment with a strong acid such as p-toluenesulfonic acid in boiling toluene. Other strong acids such as sulfuric acid, aqueous hydrobromic acid, etc. may be used.

B. A compound of formula XII [See Original Patent for Chemical Structure Diagram] XII

is reacted with a compound of formula XIII [See Original Patent for Chemical Structure Diagram] XIII

wherein M, T, V, X, k, and B are as previously defined, ring W is in accordance with formulas II to VI, L<2 > is a leaving group and L<3 > is a leaving group (which also acts as an activating group in formula XIII), to produce a compound of formula I, a compound of formula Ib [See Original Patent for Chemical Structure Diagram] Ib

or a mixture of compounds of formulas I and Ib, and if only a compound of formula Ib is produced, followed by converting the compound of formula Ib to a compound of formula I by treatment of the compound of formula Ib with strong acid, or if a mixture of compounds of formulas I and Ib was produced, optionally followed by treatment of the mixture with strong acid to convert the compound of formula Ib to a compound of formula I.

Compounds of formula XII are known or may be prepared by known methods. The choice of leaving groups L<2 > is not critical. L<2 > may, for example, be Cl, Br or -OSO2R, wherein R is phenyl, alkyl, -CF3, etc. For example, known compounds of the formula [See Original Patent for Chemical Structure Diagram] XIIa

may be converted to compounds of the formula [See Original Patent for Chemical Structure Diagram] XIIb

for example, by reaction with $SOCl_2$ or $POCl_3$ or PCl_5 to produce compounds of formula XIIb. Compounds of formula XIIb are reacted with an appropriate primary amine, the ester group is then hydrolyzed off with, for example, base, and then the resulting compound is reacted to form the acid chloride, e.g. with thionyl chloride. For example, the following reaction scheme illustrates this process: [See Original Patent for Chemical Structure Diagram]

L<3 > is a leaving group, preferably a tertiary amino leaving group, e.g., of the formula [See Original Patent for Chemical Structure Diagram]

wherein R<u > and R<v > are alkyl, arylalkyl, heteroarylalkyl, or R<u > or R<v> , together with the nitrogen atom to which they are attached may form a 5 to 8 membered saturated ring, e.g., pyrrolidine, piperidine, or morpholine. Many enamine compounds of formula XIII are known. Others may be made by known procedures, e.g., J. Am. Chem. Soc. 76, 2029 (1954). L<3 > may also be, for example, SCH_3, e.g. from the enamine 1-methyl-2-methylmercapto-2-pyrroline.

The reaction of compounds of formulas XII and XIII is carried out in solvent, e.g., dichloromethane, benzene, toluene, etc., at temperatures ranging from -10o C. to the boiling point of the solvent. The reaction proceeds in the presence of at least 2 moles of tertiary amine base, of which one mole must be of compound formula XIII. The additional base can be extra compound XIII or a different base such as, for example, triethylamine, diisopropylethylamine, etc.

The reaction of XII and XIII may yield compounds of formula I, formula Ib, or a mixture of the two. If only a compound of forumula Ib is formed, it may be converted to a compound of formula I by treatment with a strong acid such as p-toluene-sulfonic acid in boiling toluene. Other strong acids, such as sulfuric acid, aqueous hydrobromic acid, etc., may be used.

C. A compound of formula XIV [See Original Patent for Chemical Structure Diagram] XIV

is reacted with a compound of formula XV [See Original Patent for Chemical Structure Diagram] XV

wherein M, T, V, X, k, and B are a previously defined, ring W is in accordance with formulas II to VI, L<4 > is a leaving group and L<5 > is a leaving group, to produce a compound of formula I, a compound of formula Ic [See

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Original Patent for Chemical Structure Diagram] Ic

or a mixture of compounds of formulas I and Ic, and if only a compound of formula Ic is produced, followed by converting the compound of formula Ic to a compound of formula I by treatment with non-nucleophilic strong acid, or if a mixture of compounds of formulas I and Ic was produced, optionally followed by treatment of the mixture with non-nucleophilic strong acid to convert the compound of formula Ic to a compound of formula I.

Compounds of formula XIV may be made by the following reaction: [See Original Patent for Chemical Structure Diagram]

In formula XIVa, L<6 > and L<4 > are leaving groups such as Cl, Br alkoxycarbonyloxy, phenoxy, benzyloxy, trifluoromethoxy, etc.

In formulas XIVb, L<5 > is the same as L<3 > from formula XIII. The reaction of compounds XIVa and XIVb takes place in solvent, e.g., CH2Cl2, CHCl3, CCl4, benzene, toluene, etc., at - 10o C. to about 25o C., preferably to about 0o C. This reaction like process B described above requires at least 2 moles of base of which one mole must be a compound of formula XIVb.

The primary amines of formula XV are well known and commercially available or can be made by conventional means.

The reaction of compounds XIV and XV takes place in solvent, e.g., benzene, toluene, xylene, etc. at elevated temperatures up to the boiling point of the solvent. Alternatively, the reaction can be carried out in the solvent and 1 equivalent of a strong, non-nucleophilic, preferably anhydrous acid such as p-toluenesulfonic acid, trifluoromethanesulfonic acid, etc.

The reaction of compounds XIV and XV may yield compounds of formula I, formula Ic, or a mixture of the two. If only a compound of formula Ic is formed, it may be converted to a compound of formula I by treatment with a non-nucleophilic strong acid, preferably an anhydrous acid. Preferred acids for this purpose are p-toluenesulfonic acid and trifluoromethanesulfonic acid. Of course others may be used. The reaction takes place in solvent, e.g. benzene, toluene, CH2Cl2, etc. at elevated temperatures, preferably the boiling point of the solvent. Of course, this step may be omitted if the reaction of compounds XIV and XV is carried out in presence of the acid.

D. To produce a compound of formula I wherein Z is O, the dotted lines in ring t represent double bonds, and W is [See Original Patent for Chemical Structure Diagram] VII

wherein J and L and the dotted line are as previously defined, a compound of formula XXI [See Original Patent for Chemical Structure Diagram] XXI

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wherein M, T, V, X, k, and B are as previously defined, is reacted with a compound having the formula XXIIa or XXIIb [See Original Patent for Chemical Structure Diagram] XXIIb

to form compounds of formula I wherein W is of formula VII and the dotted line in formula VII represents a single bond, or with a compound of formula XXIIc

J SYMBOL OMITTED LXXIIc

to form compounds of formula I wherein W is of formula VII and the dotted line in formula VII represents a double bond. In formula XXIIb, L<7 > and L<8 > are leaving groups, e.g., halo, preferably bromo.

Compounds of formula XXIIa, XXIIb and XXIIc are well known or can be prepared by conventional methods. A process for making compounds in accordance with formula XXI is described later.

The reaction of compounds XXI with XXIIa, XXIIb, or XXIIc takes place in solvent, for example, ethyl acetate, benzene, CHCl3, at elevated temperatures, preferably the boiling point of the solvent. If a compound of formula XXIIb is employed, the reaction should take place in the presence of a base such as pyridine.

In the above processes, especially in processes A, B, and C, it is desirable and sometimes necessary to protect the groups in column 1 of the following table. Conventional protecting groups are operable. Preferred protecting groups appear in column 2 of the table. [See Original Patent for Chemical Structure Diagram]

Of course other protecting groups well known in the art may be used. After the reaction or reactions, the protecting groups may be removed by standard procedures well known in the art.

Compounds of formula I produced by processes A, B, C, or D may be converted to other compounds of formula I or to solvates or pharmaceutically acceptable salts by standard techniques. Examples of such conversions follow.

To make a compound of formula I wherein Z is O, the dotted lines in ring t represent double bonds and W is [See Original Patent for Chemical Structure Diagram] III

wherein R<1 > and R<2 > together with two adjacent carbon atoms on the ring represent aziridine, a compound of formula XVI [See Original Patent for Chemical Structure Diagram] XVI

wherein M, T, V, X, k, and B are as previously defined and W<1 > is [See Original Patent for Chemical Structure Diagram]

wherein L<9 > is alkyl or alkoxy, is reacted with alkali metal hydroxide to produce a compound of formula XVII [See Original Patent for Chemical Structure Diagram] XVII

wherein W<2 > is [See Original Patent for Chemical Structure Diagram]

The reaction is carried out in solvent, e.g., ethanol-water.

Compounds of formula XVI are produced by the following reaction sequence [See Original Patent for Chemical Structure Diagram]

wherein W<3 > is [See Original Patent for Chemical Structure Diagram]

Other suitable bases that may be used in the last step are NaH and lithium diisopropylamide. The reaction may be carried out in a non-nucleophilic aprotic solvent such as tetrahydrofuran or benzene. Since a mixture of compounds in accordance with formula XVII is produced, pure compounds may be isolated if desired by using standard techniques.

To make compounds of formula XVII, wherein W<2 > is [See Original Patent for Chemical Structure Diagram]

the position of the hydroxyl on formula XVIIa is shifted by standard techniques so that the starting compound has the formula XVIIe [See Original Patent for Chemical Structure Diagram] XVIIe

The above described reaction sequence is then followed.

To produce a compound of formula I wherein Z is O, the dotted lines in ring t represent double bonds, and W is [See Original Patent for Chemical Structure Diagram]

wherein R<1 > and R<2 > together with two adjacent carbon atoms on the ring represent an epoxide ring, a compound of formula XVIII [See Original Patent for

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Chemical Structure Diagram] XVIII

wherein W<4 > is [See Original Patent for Chemical Structure Diagram]

is reacted with a per acid to produce a compound of formula XIX [See Original Patent for Chemical Structure Diagram] XIX

wherein W<5 > is [See Original Patent for Chemical Structure Diagram]

The production of compounds of formula XVIII has been described in the previous process.

Per acids that may be reacted with compounds of formula XVIII include, for example, meta-chloroperbenzoic acid, peracetic acid, and trifluoroperacetic acid. The reaction takes place at 0o C. to room temperature in solvents such as $CHCl_3$, CH_2Cl_2, etc.

To produce a compound of formula I wherein Z is O, the dotted lines in ring t represent double bonds, and W is [See Original Patent for Chemical Structure Diagram]

wherein E is N< + > -O< - > , a compound of formula XX [See Original Patent for Chemical Structure Diagram] XX

is reacted with H_2O_2 in the presence of sodium tungstate catalyst.

Compounds of formula XX may be made by processes A, B, or C. The reaction of compound XX with H_2O_2 takes place in water, as solvent, in the presence of sodium tungstate catalyst at 0o to 25o C.

To make a compound of formula I wherein the dotted lines in ring t are not double bonds and wherein M and X are the same or different and are CH(R<a>) or NH, i.e., as in formula XXV below, a compound of formula XXIV [See Original Patent for Chemical Structure Diagram] XXIV

(wherein X and M are the same or different and are C(R<a>) or N and wherein B, k and W are as previously defined) is hydrogenated to form a compound of formula XXV [See Original Patent for Chemical Structure Diagram] XXV

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The reaction with hydrogen gas may be carried out over 10% Pd/C catalyst in glacial acetic acid or other suitable solvent at about room temperature. The pressure may range from 1 to 4 atmospheres or higher. The temperature may range from room temperature to 100o C. or higher.

To form a compound of formula I wherein at least one of M and X represents N(A) wherein A is as defined previously but other than hydrogen, and the dotted lines in ring t are not double bonds, a compound of formula XXV [See Original Patent for Chemical Structure Diagram] XXV

wherein at least one of M and X is NH and W is as defined previously, is reacted with a compound of formula XXVI

L<10> A<1XXVI >

wherein L<10 > is a leaving group and A<1 > is a radical in accordance with the previous definitions of A, but other than hydrogen.

In the formula XXVI, if A<1 > is alkyl, L<10 > may be iodine, chlorine, bromine, etc. The reaction of XXV with XXVI requires a base, e.g., NaH, and a solvent, e.g., dimethylformamide. The temperature can range from 0o to 50o C.

If A<1 > is other than alkyl, L<10 > is preferably chlorine or bromine, the solvent is toluene, CH2C12 or benzene, and the base is pyridine or triethylamine. The temperature may be 0o to 50o C.

To make a compound of formula I wherein Z is S a compound of formula I wherein Z is O is reacted with P2S5 or Lawesson's reagent, or other reagent capable of introducing sulfur in place of oxygen.

The reaction may take place at elevated temperature in pyridine or other suitable solvent. Lawesson's reagent has the formula [See Original Patent for Chemical Structure Diagram]

Numerous conversions of a compound of formula I to another compound of formula I are possible. Many of the examples illustrate such conversions.

Compounds wherein Z represents NR<e > or N(OR<i>) may be prepared by reacting the compounds wherein Z is oxygen first with an oxaphile such as SOC12, POC13, PC15, etc., and then with the appropriate amine or hydroxylamine.

The compounds of this invention can be used to treat allergies and their preferred use is for treating allergic chronic obstructive lung diseases. Chronic obstructive lung disease as used herein means disease conditions in which the passage of air through the lungs is obstructed or diminished such as is the case in asthma, bronchitis and the like.

The anti-allergy method of this invention is identified by tests which measure a compound's inhibition of anaphylactic bronchospasm in sensitized guinea pigs having antigen-induced SRS-A mediated bronchoconstriction. Allergic bronchospasm was measured in actively sensitized guinea pigs by a modification

of the procedure of Konzett and Rossler, Arch. Exptl. Pathol. Pharmakol., 194, pp. 71-74 (1940). Male Hartley guinea pigs were sensitized with 5 mg ovalbumin injected ip and 5 mg injected sc in 1 ml saline on day 1 and 5 mg ovalbumin injected ip on day 4. The sensitized animals were used 3-4 weeks later. To measure anaphylactic bronchospasm, sensitized guinea pigs were fasted overnight and the following morning were anesthetized with 0.9 ml/kg ip of dialurethane, The trachea and jugular vein were cannulated and the animals were ventilated by a Harvard rodent respirator. A side arm to the tracheal cannula was connected to a Harvard pressure transducer to obtain a continuous measure of intratracheal pressure. An increase in intratracheal pressure was taken as a measure of bronchoconstriction. Each guinea pig was injected iv with 1 mg/kg propranolol, 5 mg/kg indomethacin and 2 mg/kg mepyramine given together in a volume of 1 ml/kg. Fifteen minutes later, the animals were challenged with antigen (0.5 percent ovalbumin) delivered as an aerosol generated from a DeVilbiss Model 65 ultrasonic nebulizer and delivered through the tracheal cannula for 30 seconds. Bronchoconstriction was measured as the peak increase in intratracheal pressure occurring within 15 minutes after antigen challenge. For example, the compound 10-(3-chlorophenyl)-6,7,8,9-tetrahydrobenzo[b][1,8]naphthyridin-5(10H)-one (Compound B), was found to inhibit anaphylactic bronchospasms in such test procedure when given at an oral dose of 0.2 mg/kg. Said compound was also found to inhibit allergen-induced SRS-A and histamine release from sensitized guinea pig lung tissue.

The compounds are effective non-adrenergic, non-antichloinergic antianaphylactic agents. The compounds may be administered by any conventional mode of administration for treatment of allergic reactions employing an effective amount of a compound of formula I for such mode. For example, when administered orally they are active at doses from about 0.2 to 10 mg/kg of body weight; when administered parenterally, e.g., intravenously, the compounds are active at dosages of from about 0.1 to 5 mg/kg body weight; when administered by inhalation (aerosol or nebulizer) the compounds are active at dosages of about 0.1 to 10 mg per puff, one to four puffs may be take every 4 hours.

The compounds of this invention are also useful for the treatment of inflammation; thus, they are useful for the treatment of: arthritis, bursitis, tendonitis, gout and other inflammatory conditions. The anti-inflammatory use of the compounds of the present invention may be demonstrated by the Reversed Passive Arthus Reaction (RPAR)-PAW technique as set forth below using male Lewis rats (obtained from Charles River Breeding Laboratories) weighing 180-220 grams. The potency of the compounds is determined using indomethacin as the standard. On the basis of the test results, an oral dosage range of about 5 milligrams per kilogram of body weight per day to about 50 milligrams per kilogram of body weight per day in divided doses taken at about 4 hour intervals is recommended, again with any of the conventional modes of administration for treatment of inflammation being suitable.

The dosage to be administered and the route of administration depends upon the particular compound used, the age and general health of the patient and the severity of the inflammatory condition. Thus, the dose ultimately decided upon must be left to the judgment of a trained physician. The anti-inflammatory activity may be demonstrated by the following test procedures:
Reversed Passive Arthus Reaction (RPAR) Animals, Materials and Methods

Male Lewis inbred albino rats weighing 180-220 grams obtained from Charles

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River Breeding Laboratories are used in these experiments. The rats are housed 3 animals/cage and food and water are allowed ad libitum. The animals are numbered 1-3 in each cage and color marked for identification purposes.

All reagents and drugs are prepared just prior to the study. Crystallized and lyophilized bovine serum albumin (BSA), obtained from Sigma Chemical Company, is solubilized without shaking in cold sterile pyrogen free saline (10 mg/ml). Lyophilized anti-bovine serum albumin (IgG Fraction), obtained from Cappel Laboratories, is suspended in sterile distilled water and diluted with cold pyrogen free saline (PFS) just prior to use. The final concentratoion of anti-bovine serum albumin is 0.5 mg/ml of PFS. Both BSA and anti-BSA solutions are iced during use. Drugs are suspended or solubilized in an aqueous solution of methyl cellulose (MC) with a homogenizer just prior to administration.

Groups of animals (6/group) are dosed with drug in MC by gavage one hour prior to sensitization with BSA. Controls are given MC alone and drug-standard is usually included in each assay for verification purposes. Drugs are prepared so as to provide a dose for a 200 gram animal which is equivalent to the mg/kg dose for the experiment. Thus each rat receives an oral dose in a volume of approximately 2.0 cc. One hour after dosing the animals are lightly anesthetized with ether and sensitized by injecting into the penile vein 0.2 ml of PFS containing 1.0 mg of BSA. One hour later they are injected in the plantar region of one hind paw with 0.1 ml of PFS containing 0.1 mg of the anti-bovine serum albumin. Immediately after the subplantar injection, the injected paw is dipped (up to the lateral maleolus) into the mercury well of a plethysmograph. The volume of mercury displaced is converted to weight and recorded. This value is considered to be the control paw volume for the animal. Paw volumes are also recorded with a plethysmograph during the development of the inflammation at 2 and 4 hours post-challenge. Compounds B, C and D provided ED50 values of about 0.4, 0.1 and 0.4 mg/kg, respectively, p.o. in this procedure.

Another procedure for testing for acute anti-inflammatory activity measures the reverse passive Arthus reaction in the pleural cavity of rats as described in Myers et al, Inflammation, Vol. 9, No. 1, 1985, pp. 91-98. Compounds B and C provide ED50 values of about 0.4 mg/kg and 0.1 mg/kg, respectively, p.o. in such procedure.

The compounds of this invention are also useful in the treatment of peptic ulcers. They display chemotherapeutic activity which enables them to relieve the symptoms of peptic ulcer disease, stress ulceration, and promote healing of gastric and/or duodenal ulcers. The compounds are also useful as conjunctive therapeutic agents for coadministration with such anti-inflammatory/analgesic agents as aspirin, indomethacin, phenylbutazone, ibuprofen, naproxen, tolmetin and other agents. The compounds of this invention prevent the untoward side effects of irritation and damage to the gastrointestinal tract caused by such agents. The anti-ulcer activity of the compounds of this invention is identified by tests which measure their cytoprotective effect in rats.

The compounds of this invention may be evaluated for their antiulcer activity characteristics by the procedures which measure the cytoprotective effect in rats e.g., as described in Chiu et al., Archives Internationales de Pharmacodynamie et de Therapie, 270, 128-140 (1984). Compound A at 10 mg/kg provided an 82% inhibition of Indomethacin-induced gastric ulcers.

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In the treatment of peptic ulcer disease, and the prevention and treatment of drug-induced gastric ulceration, the active compounds of this invention can be administered in conventional unit dosage forms such as tablets, capsules, pill, powders, granules, sterile parenteral solutions or suspensions, suppositories, mechanical delivery devices, e.g., transdermal, and the like. The compounds of this invention may be administered at doses of about 0.3 to about 30 mg/kg, preferably, from about 2 to about 15 mg/kg, of body weight per day. Preferably, the total dosages are administered 2-4 divided doses per day.

The compounds of the invention are also useful as antihypertensive agents in the treatment of hypertension. The compounds effectively lower blood pressure in spontaneously hypertensive rats (SHR), an animal model of human essential hypertension, without affecting the blood pressure of normotensive rats. This activity may be demonstrated by the procedure described below.

Male spontaneously hypertensive rats or normotensive Sprague-Dawley rats were used. Blood pressure is measured according to standard procedures as described in detail in Baum T., Sybertz E. J., Watkins R. W., et al., Antihypertensive activity of SCH 31846, a non-sulfhydryl angiotensin-converting enzyme inhibitor. J. Cardiovas. Pharmacol. 5:655-667, 1983.

Animals are allowed at least 1.5-2 hours equilibration prior to experimentation. Test drugs are administered orally in a methylcellulose vehicle in a volume of 2 ml/kg and blood pressure is monitor for 4 hours following dosing. Compound A above at oral dosages of 10 and 30 mg/kg, reduced blood pressure significantly by - 21 +/- 4 (mean +/- SEM) and - 35 +/- 4 mm Hg, respectively, in the spontaneously hypertensive rats. In contrast, Compound A did not lower blood pressure in the normotensive Sprague Dawley rats. Compounds B and C at an oral dosage of 30 mg/kg lowered blood pressure by - 19 +/- 2 and - 24 +/- 2 mm Hg, respectively, in the SHR and caused negligible changes in blood pressure of normotensive Sprague Dawley rats.

The dosage range for the antihypertensive method of the invention may vary from about 3 to about 100 mg/kg, preferably about 10 to about 30 mg/kg per day, in divided doses if desired. The dose will be varied depending on a number of factors, including inter alia the hypertensive disease being treated, the patient, the potency of the particular compound employed, etc. The compounds of formula I can be administered by conventional modes, e.g. orally, intraveneously, etc., in any conventional form for such purpose such as solutions, capsules, tablets, pills, powders, sterile parenteral solutions or suspensions, transdermal compositions or the like.

The compounds of formula I are useful in the treatment of hyperproliferative skin disease, e.g., psoriasis, in mammals, e.g., humans, which may be demonstrated by the Arachidonic Acid Mouse Ear Test as described below.
Arachidonic Acid Mouse Ear Test, Materials and Methods

Charles River, female, CD, (SD) BR mice, 6 weeks old, are caged 8/group and allowed to acclimate 1-3 weeks prior to use.

Arachidonic acid (AA) is dissolved in reagent grade acetone (2 mg/0.01 ml) and stored at - 20o C. for a maximum of 1 week prior to use. Inflammatory reactions are induced by apply 10 ml of AA to both surfaces of one ear (4 gm total).

Test drugs are dissolved in either reagent grade acetone or aqueous ethanol (only if insoluble in acetone) at the same doses selected by Opas et al., Fed. Proc. 43, Abstract 2983, p. 1927 (1984) and Young et al., J. Invest. Dermatol. 82, pp. 367-371 (1984). These doses are employed to ensure maximum responses and to overcome any difference in topical absorption which could occur with any drug applied in an aqueous ethanol vehicle. The test drug is applied 30 minutes prior to challenge with AA.

The severity of the inflammation is measured as a function of increased ear weight. A 6 mm punch biopsy is removed 1 hour after AA challenge and weighed to the nearest 1.0 mg. Means +/- standard error and all possible comparisons are made via Duncan's Multiple Range Statistic.
Compounds A, B, and C provided ED50 values of 0.15 mg, 0.07 mg and 0.01 mg, respectively in the above test procedure.

As a result of the topical administration of a compound of formula I, a remission of the symptoms of the psoriatic patient, in most cases, can be expected. Thus, one affected by psoriasis can expect a decrease in scaling, erythema, size of the plaques, pruritus and other symptoms associated with psoriasis. The dosage of medicament and the length of time required for successfully treating each individual psoriatic patient may vary, but those skilled in the art of medicine will be able to recognize these variations and adjust the course of therapy accordingly.

Included within the invention are preparations for topical application to the skin whereby the compounds having structural formula I are effective in the treatment and control of skin diseases characterized by rapid rates of cell proliferation and/or abnormal cell proliferation, e.g., psoriasis.

In a preferred method of treating hyperproliferative skin diseases, a pharmaceutical formulation comprising a compound of formula I, (usually in concentrations in the range of from about 0.001 percent to about 10 percent, preferably from about 0.1 percent to about 5 percent) together with a non-toxic, pharmaceutically acceptable topical carrier, is applied several times daily to the affected skin until the condition has improved. Topical applications may then be continued at less frequent intervals (e.g. once a day) to control mitosis in order to prevent return of severe disease conditions.

The compounds of the invention are also useful in the treatment of autoimmune and other immunological diseases including graft rejection in which T cell proliferation is a contributing factor to the pathogenesis of disease. The effectiveness of these compounds as immunosuppressing agents may be demonstrated by the following tests which involve the inhibition of T cell functions using these compounds.
GRAFT VS. HOST REACTION (GVHR)

To induce a GVHR, C57 B1/6XA/J(F6AF1) male mice were injected intravenously with parental (C57B1/6J) spleen and lymph node cells. The compound (Compound A) was then administered orally for 10 days beginning on the day prior to the cell transfer. On the day following the last treatment, the animals were sacrificed, and their spleens were excised and weighed. The enlargement of the spleen of the host is a result of a GVHR. To some extent it is the host's cells which infiltrate and enlarge the spleen although they do this because of the presence

of graft cells reacting against the host. The amount of spleen enlargement, splenomegaly, is taken as a measure of the severity of the GVHR.

In carrying out the GVHR the animal in the experimental group is injected with parental cells, cells of the same species but of different genotype, which cause a weight increase of the spleen. The animal in the control group is injected with syngeneic cells, genetically identical cells which do not cause a weight increase of the spleen. The effectiveness of the compounds administered to the mice in the experimental group is measured by comparing the spleen weight of the untreated and treated GVH animal with that of the syngeneic control. Compound B reduced spleen weight by 12%, 29% and 100% at doses (mg/kg) of 25, 50 and 100, respectively, as compared to the untreated animals; while Compound C reduced spleen weight by 46%, 129% and 100% at doses (mg/kg) of 25, 50 and 100, respectively, compared to untreated animals.

SPLENIC ATROPHY

The immunosuppressive activity of the compounds may also be shown by a decrease in spleen weight after dosing BDF1 mice orally with the drug for seven (7) consecutive days. The mice are sacrificed on the eighth day. The percent decrease in spleen weight is measured for each dosage level. In this procedure, Compound B provided a 27%, 25% and 24% spleen weight decrease at dosage levels of 25, 50 and 100 mg/kg, respectively; while Compound C provided a 31%, 35% and 33% spleen weight decrease at dosage levels of 25, 50 and 100 mg/kg, respectively.

As noted above, the subject compounds possess acute anti-allergy and anti-inflammatory activities. For example, Compounds B and C have ED50 values of less than about 0.5 mg/kg and 5 mg/kg, respectively, p.o. in tests measuring the inhibition of anaphylactic bronchospasm in sensitized guinea pigs having antigen-induced broncho-constriction and ED50 values of about 0.4 mg/kg and 0.1 mg/kg, respectively, p.o. in tests measuring the reverse passive Arthus reaction in the pleural cavity of rats (as described by Myers et al., Inflammation, Vol. 9, No. 1, 1985, pp. 91-98). Compounds B and C have ED50 values of greater than about 50 mg/kg and 25 mg/kg, respectively, in the GVHR test as described above. These results for Compound B and C and similar results obtained for other compounds of formula I tested to date indicate that an immunosuppressive effective dose for such compounds is several times or more their anti-inflammatory and anti-allergy effective doses.

The usual dosage range for the immunosuppressive method of the invention with the compounds of formula I in a 70 kg mammal is an oral dose of about 0.1 to 250 mg/kg, preferably 0.1 to 150 mg/kg, in 3 or 4 divided doses per day. Of course, the dose will be regulated according to the potency of compound employed, the immunological disease being treated, and the judgment of the attending clinician depending on factors such as the degree and the severity of the disease state and age and general condition of the patient being treated.

To treat immunological diseases, the active compounds of formula I can be administered in unit dosage forms such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, suppositories, transdermal compositions and the like. Such dosage forms are prepared according to standard techniques well known in the art.

Some of the compounds of this invention are also useful in preventing cardiac

anaphylaxis.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to about 70 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethyl-cellulose, a low melting wax, cocoa butter and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in polyethylene glycol and/or propylene glycol, which may contain water. Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Formulations for topical application, e.g., for use in treating hyperproliferative skin diseases, may include the above liquid forms, creams, aerosols, sprays, dusts, powders, lotions and ointments which are prepared by combining an active ingredient according to this inventions with conventional pharmaceutical diluents and carriers commonly used in topical dry, liquid, cream and aerosol formulations. Ointment and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Such bases may, thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as peanut oil or castor oil. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminum stearate, cetostearyl alcohol, propylene glycol, polyethylene glycols, woolfat, hydrogenated lanolin, beeswax, etc.

Lotions may be formulations with an aqueous or oily base and will, in

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general, also include one or more of the folloiwing, namely, stabilizing agents, emulsifying agents, dispersing agents, suspending agents, thickening agents, coloring agents, perfumes and the like.

Powders may be formed with the aid of any suitable powder base, e.g., talc, lactose, starch, etc. Drops may be formulated with an aqueous base or non-aqueous base also comprising one or more dispersing agents, suspending agents, solubilizing agents, etc.

The topical pharmaceutical compositions according to the invention may also include one or more preservatives or bacteriostatic agents, e.g., methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chlorides, etc.

The topical pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, particularly antibiotics, anesthetics, analgesics and antipruritic agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternatively, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerine, propylene glycol and the like as well as mixtures thereof. Naturally, the solvent utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet or tablet itself or it can be the appropriate number of any of these in packaged form.

When administered parenterally, e.g. intravenously, the compounds are administered at a dosage range of about 1-30 mg/kg of body weight in single or multiple daily doses.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 100 mg according to the particular application and the potency of the active ingredient. The compositions can, if desired, also contain other therapeutic agents.

The dosages may be varied depending upon the requirements of the patient, the severity of the condition being treated and the particular compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

DETDESC:

The following examples are intended to illustrate, but not to limit, the present invention.

PREPARATIVE EXAMPLE 1

Dissolve 2-chloronicotinoyl chloride (0.10 mole) in CHCl3 (90 ml). Add the resulting solution to a 5o C. solution of triethylamine (0.10 mole) and an enamine, 1-(1-pyrrolidinyl)-1-cyclopentene (0.10 mole), dissolved in CHCl3 (90 ml). Allow C-acylation to proceed for 21 hrs., while the temperature of the reaction mixture rises to 25o after the second hour. Monitor the course of the reaction by thin-layer chromatography as needed. Wash the resulting solution with water, aqueous NaHCO3 solution, and with water. After drying, carefully evaporate solvent to obtain the enaminoketone, (2-chloro-3-pyridinyl)[2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]methanone, m.p. 102.5o-104.0o C., after recrystallization from ethyl acetate. This compound is referred to in Examples 1 and 3 below as Compound 1.

By employing the acid chloride and enamine listed in Columns 1 and 2 of Table 1 below, the compounds listed in Column 3 are prepared. In some instances CH2Cl2 is used in place of CHCl3 and the reaction time is varied. 2-Chloronicotinoyl and 2-chloro-3-pyridazinylcarbonyl chloride are available from Chemo Dynamics Inc., whereas the Aldrich Chemical Co. supplies certain enamines, e.g. 1-pyrrolidino-1-cyclopentene, 1-morpholino-1-cyclohexene, and 1-pyrrolidino-1-cyclohexene. Other enamines employed here and elsewhere in the following examples are prepared according to J. Am. Chem. Soc. 76, 2029 (1954) or other methods. For example, the indicated enamines may be prepared by the methods disclosed in the articles listed after each: 2-(1-pyrrolidino)-indene, J. Org. Chem. 26, 3761 (1961); 1-methyl-2-methylmercapto-2-pyrroline, Org. Syn. 62, 158 (1984) and Liebigs Ann. Chem. 725, 70 (1969); 4-carbethoxy-1-(1-pyrrolidino)-cyclohexene, 1,2-dicarbethoxy-4-(1-pyrrolidino)-4-pyrroline, 1-acetyl-3-(1-pyrrolidino)-2-pyrroline, and 1-acetyl-4-(1-pyrrolidino)-1,2,5,6-tetrahydropyridine, J. Am. Chem. Soc. 76, 2029, (1954); and 5,6-dihydro-4-(1-pyrrolidino)-2H-thiopyran, Zh. Organ. Khim., 1, 1108 (1965). The following ketone starting materials for the enamines may be prepared, for example, by the methods disclosed in the articles listed after each: 4-carbethoxycyclohexanone, Synth. Commun. 15, 541 (1985); 1,2-dicarbethoxy-4-pyrrolidinone, J. Org. Chem. 38, 3487 (1973); 1-acetyl-3-pyrrolidinone, J. Med. Chem. 5, 762 (1962). TABLE 1 [See Original Patent for Chemical Structure Diagram]

PREPARATIVE EXAMPLE 2

Add equimolar amounts of ethyl glycinate hydrochloride, triethylamine, and (2-chloro-3-pyridinyl) [2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]methanone to t-butyl alcohol (170 ml per 0.020 mole of amine). Reflux the resulting mixture for 34 hrs, monitoring the reaction by thin-layer chromatography as needed. Cool the reaction mixture, and evaporate solvent. Wash a CHCl3 solution of the residue with water and with saturated aqueous NaCl solution. After drying the organic solution, evaporate the solvent to obtain the resulting enaminoketone, (2-chloro-3-pyridinyl) [2-(1-ethoxycarbonylmethanaminyl)-1-cyclopenten-1-yl] methanone, m.p. 114.5o-117.5o C., after recrystallization from isopropanol.
EXAMPLE 1

Dissolve the primary amine, 3-nitroaniline, and the enaminoketone (Compound 1 above) in benzene containing anhydrous p-toluenesulfonic acid. Let the molar ratio of the primary amine to enaminoketone be about 1.25 and that of acid to enaminoketone be 1. Use enough benzene to give a solution that is initially 1M in enaminoketone. Reflux the resulting solution 26 hours, and monitor the course of the reaction by thin-layer chromatography as needed. Cool the reaction mixture, evaporate the solvent, and dissolve the residue in CHCl3. Wash the CHCl3 solution with water, aqueous NaHCO3 solution, dilute aqueous HCl solution, and with water. After drying the CHCl3 solution, evaporate solvent to obtain the resulting naphthyridinone,
9-(3-nitrophenyl)-6,7,8,9-tetrahydro-5H-cyclopenta[b][1,8]naphthyridin-5-one, m.p. 276o-277o C., after recrystallization from CH3CN.
EXAMPLE 2

Dissolve 3-chloroaniline (0.0733 mol) and the enaminoketone (Compound 2 in Table 1 above) (0.0539 mol) in benzene (50 ml) containing p-toluenesulfonic acid monohydrate (0.0523 mol). Reflux the solution for 18 hours, removing water with a Dean Stark trap. Cool the resulting mixture and evaporate the solvent, dissolving the residue in CHCl3. Wash the CHCl3 solution with water, 2N HCl, water, in NaHCO3, and with water. Dry and filter the CHCl3 solution, and evaporate the solvent to give
10-(3-chlorophenyl)-6,7,8,9-tetrahydrobenzo[b][1,8]naphthyridin-5(10H)-one, m.p. 195o-198o C. after crystallization from CH3CN.

By employing the primary amine the enaminoketone as indicated in Columns 1 and 2 of Table 2 below, the naphthyridinones or pyrazinopyridones as indicated in Column 3 of Table 2 are prepared by basically the same methods as described in Examples 1 and 2. TABLE 2

[See table in original]

By employing the primary amines and enaminoketones as indicated in Columns 1 and 2 of Table 3 below, the compounds of Column 3 may also be prepared by basically the same method. TABLE 3 [See Original Patent for Chemical Structure Diagram]

EXAMPLE 3

Mix aniline and the enaminoketone (Compound 1 above) in a molar ratio of

1.25:1, and heat the mixture 51 hours at 110o C. and 24 hours at 125o C. Cool the resulting mixture, dissolve it in CHCl3, and treat the CHCl3 solution as described in Example 1 above to produce 9-phenyl-6,7,8,9-tetrahydro-5H-cyclopenta[b]-[1,8]naphthyridin-5-one, m.p. 235o-237o C., after recrystallization from CH3CN.

By employing the primary amines and enaminoketones as indicated in Columns 1 and 2 of Table 4 below, the compounds listed in Column 3 thereof are prepared by basically the same method varying the reaction time from 4.5-100 hrs. and the temperature from 110o-130o C. as necessary. If the amine used in this example is hydrazine, then use a molar ratio of hydrazine to enaminoketone of 8.5:1. TABLE 4 [See Original Patent for Chemical Structure Diagram]

EXAMPLE 4

Reflux a solution of (2-bromophenyl) [2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]-methanone (14.1 g) (from Preparative Example 1) in benzene (100 ml) containing aniline (4.5 ml) and p-toluenesulfonic acid monohydrate (8.8 g) for 19 hrs. Remove water continuously with a Dean-Stark trap. Wash the cooled solution with water, 1M NaHCO3 solution, and with water. Dry the benzene solution, filter it, and evaporate the solvent. Crystallize to obtain (2-bromophenyl) [2-(phenylamino)-1-cyclopenten-1-yl]-methanone, m.p. 106.5o-108.5o from CH3CN.

Reflux a mixture of (2-bromophenyl) [2-(phenylamino)-1-cyclopenten-1-yl]-methanone (5.8 mmol), potassium tert.-butoxide (0.71 g), and tert.-butanol (25 ml) under nitrogen for 1 hr. Monitor the ensuing reaction by thin-layer chromatography, and cool the mixture when reaction is complete. Evaporate tert.-butanol, add water (25 ml) to the residue, and filter off the product, 1,2,3,4-tetrahydro-4-phenyl-9H-cyclopenta[b]quinolin-9-one, m.p. 265-267, after crystallization from CH3CN/CHCl3.

PREPARATIVE EXAMPLE 3

Prepare 2-(3-chlorophenylamino)pyridinyl-3-carbonyl chloride as follows. Add excess thionyl chloride (0.6 ml per mmol of acid) to 2-(3-chlorophenylamino)pyridinyl-3-carboxylic acid (0.38 mol), and allow the resulting mixture to stand or stir at 25o C. for 2 hours. To catalyze the reaction, add N,N-dimethyl formamide (0.008 ml per mmol of acid) as needed. When acid chloride formation is complete, evaporate excess thionyl chloride. Remove any traces of the reagent by adding benzene and evaporating it. To ensure that solid products are relatively dense and therefore easily manipulated, carry out evaporation at an elevated temperature; a temperature not exceeding 50o C. is suitable. Wash the resulting solid with benzene and petroleum ether to give 2-(3-chlorophenylamino)pyridinyl-3-carbonylchloride, m.p. 110o-114o C.

By employing the 2-arylaminopyridinyl-3-carboxylic acid listed below in Table 5, basically the same process may be used to prepare the corresponding carbonyl chlorides thereof. The 2-arylaminopyridinyl-3-carboxylic acids that are needed to apply this method may be prepared according to U.S. Pat. No. *3,689,653*. TABLE 5 [See Original Patent for Chemical Structure Diagram]

EXAMPLE 5

Add equimolar amounts of the enamine, 1-acetyl-4-(1-pyrrolidino)-1,2,5,6-tetrahydropyridine (40 mmol) and triethylamine (43 mmol), both dissolved in dichloromethane (27 ml per mmol of the enamine), to a stirred, cooled solution of an equimolar amount of 2-(3-chlorophenylamino)pyridinyl-3-carbonyl chloride in dichloromethane (175 ml). When addition is complete, allow the reaction mixture to stir for 1 hour at 0o C. and for 20 hours at 25o C. Wash the organic solution with water, dilute aqueous sodium bicarbonate solution and with water. Dry the organic solution over a suitable dessicant, filter, and evaporate dichloromethane and any excess triethylamine. Crystallize the residue, 7-acetyl-10-(3-chlorophenyl)-6,8,9,10-tetrahydropyrido[2,3-b][1,6]naphthyridin-5(7H)-one, m.p. 238o-242o C. after recrystallization from CH3CN. Alternatively, the residue may be triturated with ether, and the solid collected on a filter and then crystallized.

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River Breeding Laboratories are used in these experiments. The rats are housed 3 animals/cage and food and water are allowed ad libitum. The animals are numbered 1-3 in each cage and color marked for identification purposes.

All reagents and drugs are prepared just prior to the study. Crystallized and lyophilized bovine serum albumin (BSA), obtained from Sigma Chemical Company, is solubilized without shaking in cold sterile pyrogen free saline (10 mg/ml). Lyophilized anti-bovine serum albumin (IgG Fraction), obtained from Cappel Laboratories, is suspended in sterile distilled water and diluted with cold pyrogen free saline (PFS) just prior to use. The final concentratoion of anti-bovine serum albumin is 0.5 mg/ml of PFS. Both BSA and anti-BSA solutions are iced during use. Drugs are suspended or solubilized in an aqueous solution of methyl cellulose (MC) with a homogenizer just prior to administration.

Groups of animals (6/group) are dosed with drug in MC by gavage one hour prior to sensitization with BSA. Controls are given MC alone and drug-standard is usually included in each assay for verification purposes. Drugs are prepared so as to provide a dose for a 200 gram animal which is equivalent to the mg/kg dose for the experiment. Thus each rat receives an oral dose in a volume of approximately 2.0 cc. One hour after dosing the animals are lightly anesthetized with ether and sensitized by injecting into the penile vein 0.2 ml of PFS containing 1.0 mg of BSA. One hour later they are injected in the plantar region of one hind paw with 0.1 ml of PFS containing 0.1 mg of the anti-bovine serum albumin. Immediately after the subplantar injection, the injected paw is dipped (up to the lateral maleolus) into the mercury well of a plethysmograph. The volume of mercury displaced is converted to weight and recorded. This value is considered to be the control paw volume for the animal. Paw volumes are also recorded with a plethysmograph during the development of the inflammation at 2 and 4 hours post-challenge. Compounds B, C and D provided ED50 values of about 0.4, 0.1 and 0.4 mg/kg, respectively, p.o. in this procedure.

Another procedure for testing for acute anti-inflammatory activity measures the reverse passive Arthus reaction in the pleural cavity of rats as described in Myers et al, Inflammation, Vol. 9, No. 1, 1985, pp. 91-98. Compounds B and C provide ED50 values of about 0.4 mg/kg and 0.1 mg/kg, respectively, p.o. in such procedure.

The compounds of this invention are also useful in the treatment of peptic ulcers. They display chemotherapeutic activity which enables them to relieve the symptoms of peptic ulcer disease, stress ulceration, and promote healing of gastric and/or duodenal ulcers. The compounds are also useful as conjunctive therapeutic agents for coadministration with such anti-inflammatory/analgesic agents as aspirin, indomethacin, phenylbutazone, ibuprofen, naproxen, tolmetin and other agents. The compounds of this invention prevent the untoward side effects of irritation and damage to the gastrointestinal tract caused by such agents. The anti-ulcer activity of the compounds of this invention is identified by tests which measure their cytoprotective effect in rats.

The compounds of this invention may be evaluated for their antiulcer activity characteristics by the procedures which measure the cytoprotective effect in rats e.g., as described in Chiu et al., Archives Internationales de Pharmacodynamie et de Therapie, 270, 128-140 (1984). Compound A at 10 mg/kg provided an 82% inhibition of Indomethacin-induced gastric ulcers.

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In the treatment of peptic ulcer disease, and the prevention and treatment of drug-induced gastric ulceration, the active compounds of this invention can be administered in conventional unit dosage forms such as tablets, capsules, pill, powders, granules, sterile parenteral solutions or suspensions, suppositories, mechanical delivery devices, e.g., transdermal, and the like. The compounds of this invention may be administered at doses of about 0.3 to about 30 mg/kg, preferably, from about 2 to about 15 mg/kg, of body weight per day. Preferably, the total dosages are administered 2-4 divided doses per day.

The compounds of the invention are also useful as antihypertensive agents in the treatment of hypertension. The compounds effectively lower blood pressure in spontaneously hypertensive rats (SHR), an animal model of human essential hypertension, without affecting the blood pressure of normotensive rats. This activity may be demonstrated by the procedure described below.

Male spontaneously hypertensive rats or normotensive Sprague-Dawley rats were used. Blood pressure is measured according to standard procedures as described in detail in Baum T., Sybertz E. J., Watkins R. W., et al., Antihypertensive activity of SCH 31846, a non-sulfhydryl angiotensin-converting enzyme inhibitor. J. Cardiovas. Pharmacol. 5:655-667,1983.

Animals are allowed at least 1.5-2 hours equilibration prior to experimentation. Test drugs are administered orally in a methylcellulose vehicle in a volume of 2 ml/kg and blood pressure is monitor for 4 hours following dosing. Compound A above at oral dosages of 10 and 30 mg/kg, reduced blood pressure significantly by - 21 +/- 4 (mean +/- SEM) and - 35 +/- 4 mm Hg, respectively, in the spontaneously hypertensive rats. In contrast, Compound A did not lower blood pressure in the normotensive Sprague Dawley rats. Compounds B and C at an oral dosage of 30 mg/kg lowered blood pressure by - 19 +/- 2 and - 24 +/- 2 mm Hg, respectively, in the SHR and caused negligible changes in blood pressure of normotensive Sprague Dawley rats.

The dosage range for the antihypertensive method of the invention may vary from about 3 to about 100 mg/kg, preferably about 10 to about 30 mg/kg per day, in divided doses if desired. The dose will be varied depending on a number of factors, including inter alia the hypertensive disease being treated, the patient, the potency of the particular compound employed, etc. The compounds of formula I can be administered by conventional modes, e.g. orally, intraveneously, etc., in any conventional form for such purpose such as solutions, capsules, tablets, pills, powders, sterile parenteral solutions or suspensions, transdermal compositions or the like.

The compounds of formula I are useful in the treatment of hyperproliferative skin disease, e.g., psoriasis, in mammals, e.g., humans, which may be demonstrated by the Arachidonic Acid Mouse Ear Test as described below.
Arachidonic Acid Mouse Ear Test, Materials and Methods

Charles River, female, CD, (SD) BR mice, 6 weeks old, are caged 8/group and allowed to acclimate 1-3 weeks prior to use.

Arachidonic acid (AA) is dissolved in reagent grade acetone (2 mg/0.01 ml) and stored at - 20o C. for a maximum of 1 week prior to use. Inflammatory reactions are induced by apply 10 ml of AA to both surfaces of one ear (4 gm total).

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Test drugs are dissolved in either reagent grade acetone or aqueous ethanol (only if insoluble in acetone) at the same doses selected by Opas et al., Fed. Proc. 43, Abstract 2983, p. 1927 (1984) and Young et al., J. Invest. Dermatol. 82, pp. 367-371 (1984). These doses are employed to ensure maximum responses and to overcome any difference in topical absorption which could occur with any drug applied in an aqueous ethanol vehicle. The test drug is applied 30 minutes prior to challenge with AA.

The severity of the inflammation is measured as a function of increased ear weight. A 6 mm punch biopsy is removed 1 hour after AA challenge and weighed to the nearest 1.0 mg. Means +/- standard error and all possible comparisons are made via Duncan's Multiple Range Statistic.

Compounds A, B, and C provided ED50 values of 0.15 mg, 0.07 mg and 0.01 mg, respectively in the above test procedure.

As a result of the topical administration of a compound of formula I, a remission of the symptoms of the psoriatic patient, in most cases, can be expected. Thus, one affected by psoriasis can expect a decrease in scaling, erythema, size of the plaques, pruritus and other symptoms associated with psoriasis. The dosage of medicament and the length of time required for successfully treating each individual psoriatic patient may vary, but those skilled in the art of medicine will be able to recognize these variations and adjust the course of therapy accordingly.

Included within the invention are preparations for topical application to the skin whereby the compounds having structural formula I are effective in the treatment and control of skin diseases characterized by rapid rates of cell proliferation and/or abnormal cell proliferation, e.g., psoriasis.

In a preferred method of treating hyperproliferative skin diseases, a pharmaceutical formulation comprising a compound of formula I, (usually in concentrations in the range of from about 0.001 percent to about 10 percent, preferably from about 0.1 percent to about 5 percent) together with a non-toxic, pharmaceutically acceptable topical carrier, is applied several times daily to the affected skin until the condition has improved. Topical applications may then be continued at less frequent intervals (e.g. once a day) to control mitosis in order to prevent return of severe disease conditions.

The compounds of the invention are also useful in the treatment of autoimmune and other immunological diseases including graft rejection in which T cell proliferation is a contributing factor to the pathogenesis of disease. The effectiveness of these compounds as immunosuppressing agents may be demonstrated by the following tests which involve the inhibition of T cell functions using these compounds.

GRAFT VS. HOST REACTION (GVHR)

To induce a GVHR, C57 B1/6XA/J(F6AF1) male mice were injected intravenously with parental (C57B1/6J) spleen and lymph node cells. The compound (Compound A) was then administered orally for 10 days beginning on the day prior to the cell transfer. On the day following the last treatment, the animals were sacrificed, and their spleens were excised and weighed. The enlargement of the spleen of the host is a result of a GVHR. To some extent it is the host's cells which infiltrate and enlarge the spleen although they do this because of the presence

of graft cells reacting against the host. The amount of spleen enlargement, splenomegaly, is taken as a measure of the severity of the GVHR.

In carrying out the GVHR the animal in the experimental group is injected with parental cells, cells of the same species but of different genotype, which cause a weight increase of the spleen. The animal in the control group is injected with syngeneic cells, genetically identical cells which do not cause a weight increase of the spleen. The effectiveness of the compounds administered to the mice in the experimental group is measured by comparing the spleen weight of the untreated and treated GVH animal with that of the syngeneic control. Compound B reduced spleen weight by 12%, 29% and 100% at doses (mg/kg) of 25, 50 and 100, respectively, as compared to the untreated animals; while Compound C reduced spleen weight by 46%, 129% and 100% at doses (mg/kg) of 25, 50 and 100, respectively, compared to untreated animals.
SPLENIC ATROPHY

The immunosuppressive activity of the compounds may also be shown by a decrease in spleen weight after dosing BDF1 mice orally with the drug for seven (7) consecutive days. The mice are sacrificed on the eighth day. The percent decrease in spleen weight is measured for each dosage level. In this procedure, Compound B provided a 27%, 25% and 24% spleen weight decrease at dosage levels of 25, 50 and 100 mg/kg, respectively; while Compound C provided a 31%, 35% and 33% spleen weight decrease at dosage levels of 25, 50 and 100 mg/kg, respectively.

As noted above, the subject compounds possess acute anti-allergy and anti-inflammatory activities. For example, Compounds B and C have ED50 values of less than about 0.5 mg/kg and 5 mg/kg, respectively, p.o. in tests measuring the inhibition of anaphylactic bronchospasm in sensitized guinea pigs having antigen-induced broncho-constriction and ED50 values of about 0.4 mg/kg and 0.1 mg/kg, respectively, p.o. in tests measuring the reverse passive Arthus reaction in the pleural cavity of rats (as described by Myers et al., Inflammation, Vol. 9, No. 1, 1985, pp. 91-98). Compounds B and C have ED50 values of greater than about 50 mg/kg and 25 mg/kg, respectively, in the GVHR test as described above. These results for Compound B and C and similar results obtained for other compounds of formula I tested to date indicate that an immunosuppressive effective dose for such compounds is several times or more their anti-inflammatory and anti-allergy effective doses.

The usual dosage range for the immunosuppressive method of the invention with the compounds of formula I in a 70 kg mammal is an oral dose of about 0.1 to 250 mg/kg, preferably 0.1 to 150 mg/kg, in 3 or 4 divided doses per day. Of course, the dose will be regulated according to the potency of compound employed, the immunological disease being treated, and the judgment of the attending clinician depending on factors such as the degree and the severity of the disease state and age and general condition of the patient being treated.

To treat immunological diseases, the active compounds of formula I can be administered in unit dosage forms such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, suppositories, transdermal compositions and the like. Such dosage forms are prepared according to standard techniques well known in the art.

Some of the compounds of this invention are also useful in preventing cardiac

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anaphylaxis.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to about 70 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethyl-cellulose, a low melting wax, cocoa butter and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in polyethylene glycol and/or propylene glycol, which may contain water. Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Formulations for topical application, e.g., for use in treating hyperproliferative skin diseases, may include the above liquid forms, creams, aerosols, sprays, dusts, powders, lotions and ointments which are prepared by combining an active ingredient according to this inventions with conventional pharmaceutical diluents and carriers commonly used in topical dry, liquid, cream and aerosol formulations. Ointment and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Such bases may, thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as peanut oil or castor oil. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminum stearate, cetostearyl alcohol, propylene glycol, polyethylene glycols, woolfat, hydrogenated lanolin, beeswax, etc.

Lotions may be formulations with an aqueous or oily base and will, in

general, also include one or more of the folloiwing, namely, stabilizing agents, emulsifying agents, dispersing agents, suspending agents, thickening agents, coloring agents, perfumes and the like.

Powders may be formed with the aid of any suitable powder base, e.g., talc, lactose, starch, etc. Drops may be formulated with an aqueous base or non-aqueous base also comprising one or more dispersing agents, suspending agents, solubilizing agents, etc.

The topical pharmaceutical compositions according to the invention may also include one or more preservatives or bacteriostatic agents, e.g., methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chlorides, etc.

The topical pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, particularly antibiotics, anesthetics, analgesics and antipruritic agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternatively, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerine, propylene glycol and the like as well as mixtures thereof. Naturally, the solvent utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet or tablet itself or it can be the appropriate number of any of these in packaged form.

When administered parenterally, e.g. intravenously, the compounds are administered at a dosage range of about 1-30 mg/kg of body weight in single or multiple daily doses.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 100 mg according to the particular application and the potency of the active ingredient. The compositions can, if desired, also contain other therapeutic agents.

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The dosages may be varied depending upon the requirements of the patient, the severity of the condition being treated and the particular compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

DETDESC:

The following examples are intended to illustrate, but not to limit, the present invention.

PREPARATIVE EXAMPLE 1

Dissolve 2-chloronicotinoyl chloride (0.10 mole) in CHCl3 (90 ml). Add the resulting solution to a 5o C. solution of triethylamine (0.10 mole) and an enamine, 1-(1-pyrrolidinyl)-1-cyclopentene (0.10 mole), dissolved in CHCl3 (90 ml). Allow C-acylation to proceed for 21 hrs., while the temperature of the reaction mixture rises to 25o after the second hour. Monitor the course of the reaction by thin-layer chromatography as needed. Wash the resulting solution with water, aqueous NaHCO3 solution, and with water. After drying, carefully evaporate solvent to obtain the enaminoketone, (2-chloro-3-pyridinyl)[2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]methanone, m.p. 102.5o-104.0o C., after recrystallization from ethyl acetate. This compound is referred to in Examples 1 and 3 below as Compound 1.

By employing the acid chloride and enamine listed in Columns 1 and 2 of Table 1 below, the compounds listed in Column 3 are prepared. In some instances CH2Cl2 is used in place of CHCl3 and the reaction time is varied. 2-Chloronicotinoyl and 2-chloro-3-pyridazinylcarbonyl chloride are available from Chemo Dynamics Inc., whereas the Aldrich Chemical Co. supplies certain enamines, e.g. 1-pyrrolidino-1-cyclopentene, 1-morpholino-1-cyclohexene, and 1-pyrrolidino-1-cyclohexene. Other enamines employed here and elsewhere in the following examples are prepared according to J. Am. Chem. Soc. 76, 2029 (1954) or other methods. For example, the indicated enamines may be prepared by the methods disclosed in the articles listed after each: 2-(1-pyrrolidino)-indene, J. Org. Chem. 26, 3761 (1961); 1-methyl-2-methylmercapto-2-pyrroline, Org. Syn. 62, 158 (1984) and Liebigs Ann. Chem. 725, 70 (1969); 4-carbethoxy-1-(1-pyrrolidino)-cyclohexene, 1,2-dicarbethoxy-4-(1-pyrrolidino)-4-pyrroline, 1-acetyl-3-(1-pyrrolidino)-2-pyrroline, and 1-acetyl-4-(1-pyrrolidino)-1,2,5,6-tetrahydropyridine, J. Am. Chem. Soc. 76, 2029, (1954); and 5,6-dihydro-4-(1-pyrrolidino)-2H-thiopyran, Zh. Organ. Khim., 1, 1108 (1965). The following ketone starting materials for the enamines may be prepared, for example, by the methods disclosed in the articles listed after each: 4-carbethoxycyclohexanone, Synth. Commun. 15, 541 (1985); 1,2-dicarbethoxy-4-pyrrolidinone, J. Org. Chem. 38, 3487 (1973); 1-acetyl-3-pyrrolidinone, J. Med. Chem. 5, 762 (1962). TABLE 1 [See Original Patent for Chemical Structure Diagram]

PREPARATIVE EXAMPLE 2

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Add equimolar amounts of ethyl glycinate hydrochloride, triethylamine, and (2-chloro-3-pyridinyl) [2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]methanone to t-butyl alcohol (170 ml per 0.020 mole of amine). Reflux the resulting mixture for 34 hrs, monitoring the reaction by thin-layer chromatography as needed. Cool the reaction mixture, and evaporate solvent. Wash a CHCl3 solution of the residue with water and with saturated aqueous NaCl solution. After drying the organic solution, evaporate the solvent to obtain the resulting enaminoketone, (2-chloro-3-pyridinyl) [2-(1-ethoxycarbonylmethanaminyl)-1-cyclopenten-1-yl] methanone, m.p. 114.5o-117.5o C., after recrystallization from isopropanol.
EXAMPLE 1

Dissolve the primary amine, 3-nitroaniline, and the enaminoketone (Compound 1 above) in benzene containing anhydrous p-toluenesulfonic acid. Let the molar ratio of the primary amine to enaminoketone be about 1.25 and that of acid to enaminoketone be 1. Use enough benzene to give a solution that is initially 1M in enaminoketone. Reflux the resulting solution 26 hours, and monitor the course of the reaction by thin-layer chromatography as needed. Cool the reaction mixture, evaporate the solvent, and dissolve the residue in CHCl3. Wash the CHCl3 solution with water, aqueous NaHCO3 solution, dilute aqueous HCl solution, and with water. After drying the CHCl3 solution, evaporate solvent to obtain the resulting naphthyridinone,
9-(3-nitrophenyl)-6,7,8,9-tetrahydro-5H-cyclopenta[b] [1,8]naphthyridin-5-one, m.p. 276o-277o C., after recrystallization from CH3CN.
EXAMPLE 2

Dissolve 3-chloroaniline (0.0733 mol) and the enaminoketone (Compound 2 in Table 1 above) (0.0539 mol) in benzene (50 ml) containing p-toluenesulfonic acid monohydrate (0.0523 mol). Reflux the solution for 18 hours, removing water with a Dean Stark trap. Cool the resulting mixture and evaporate the solvent, dissolving the residue in CHCl3. Wash the CHCl3 solution with water, 2N HCl, water, in NaHCO3, and with water. Dry and filter the CHCl3 solution, and evaporate the solvent to give
10-(3-chlorophenyl)-6,7,8,9-tetrahydrobenzo[b] [1,8]naphthyridin-5(10H)-one, m.p. 195o-198o C. after crystallization from CH3CN.

By employing the primary amine the enaminoketone as indicated in Columns 1 and 2 of Table 2 below, the naphthyridinones or pyrazinopyridones as indicated in Column 3 of Table 2 are prepared by basically the same methods as described in Examples 1 and 2. TABLE 2

[See table in original]

By employing the primary amines and enaminoketones as indicated in Columns 1 and 2 of Table 3 below, the compounds of Column 3 may also be prepared by basically the same method. TABLE 3 [See Original Patent for Chemical Structure Diagram]

EXAMPLE 3

Mix aniline and the enaminoketone (Compound 1 above) in a molar ratio of

1.25:1, and heat the mixture 51 hours at 110o C. and 24 hours at 125o C. Cool the resulting mixture, dissolve it in CHCl3, and treat the CHCl3 solution as described in Example 1 above to produce 9-phenyl-6,7,8,9-tetrahydro-5H-cyclopenta[b]-[1,8]naphthyridin-5-one, m.p. 235o-237o C., after recrystallization from CH3CN.

By employing the primary amines and enaminoketones as indicated in Columns 1 and 2 of Table 4 below, the compounds listed in Column 3 thereof are prepared by basically the same method varying the reaction time from 4.5-100 hrs. and the temperature from 110o-130o C. as necessary. If the amine used in this example is hydrazine, then use a molar ratio of hydrazine to enaminoketone of 8.5:1. TABLE 4 [See Original Patent for Chemical Structure Diagram]

EXAMPLE 4

Reflux a solution of (2-bromophenyl) [2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]-methanone (14.1 g) (from Preparative Example 1) in benzene (100 ml) containing aniline (4.5 ml) and p-toluenesulfonic acid monohydrate (8.8 g) for 19 hrs. Remove water continuously with a Dean-Stark trap. Wash the cooled solution with water, 1M NaHCO3 solution, and with water. Dry the benzene solution, filter it, and evaporate the solvent. Crystallize to obtain (2-bromophenyl) [2-(phenylamino)-1-cyclopenten-1-yl]-methanone, m.p. 106.5o-108.5o from CH3CN.

Reflux a mixture of (2-bromophenyl) [2-(phenylamino)-1-cyclopenten-1-yl]-methanone (5.8 mmol), potassium tert.-butoxide (0.71 g), and tert.-butanol (25 ml) under nitrogen for 1 hr. Monitor the ensuing reaction by thin-layer chromatography, and cool the mixture when reaction is complete. Evaporate tert.-butanol, add water (25 ml) to the residue, and filter off the product, 1,2,3,4-tetrahydro-4-phenyl-9H-cyclopenta[b]quinolin-9-one, m.p. 265-267, after crystallization from CH3CN/CHCl3.

PREPARATIVE EXAMPLE 3

Prepare 2-(3-chlorophenylamino)pyridinyl-3-carbonyl chloride as follows. Add excess thionyl chloride (0.6 ml per mmol of acid) to 2-(3-chlorophenylamino)pyridinyl-3-carboxylic acid (0.38 mol), and allow the resulting mixture to stand or stir at 25o C. for 2 hours. To catalyze the reaction, add N,N-dimethyl formamide (0.008 ml per mmol of acid) as needed. When acid chloride formation is complete, evaporate excess thionyl chloride. Remove any traces of the reagent by adding benzene and evaporating it. To ensure that solid products are relatively dense and therefore easily manipulated, carry out evaporation at an elevated temperature; a temperature not exceeding 50o C. is suitable. Wash the resulting solid with benzene and petroleum ether to give 2-(3-chlorophenylamino)pyridinyl-3-carbonylchloride, m.p. 110o-114o C.

By employing the 2-arylaminopyridinyl-3-carboxylic acid listed below in Table 5, basically the same process may be used to prepare the corresponding carbonyl chlorides thereof. The 2-arylaminopyridinyl-3-carboxylic acids that are needed to apply this method may be prepared according to U.S. Pat. No. *3,689,653*. TABLE 5 [See Original Patent for Chemical Structure Diagram]

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EXAMPLE 5

Add equimolar amounts of the enamine, 1-acetyl-4-(1-pyrrolidino)-1,2,5,6-tetrahydropyridine (40 mmol) and triethylamine (43 mmol), both dissolved in dichloromethane (27 ml per mmol of the enamine), to a stirred, cooled solution of an equimolar amount of 2-(3-chlorophenylamino)pyridinyl-3-carbonyl chloride in dichloromethane (175 ml). When addition is complete, allow the reaction mixture to stir for 1 hour at 0o C. and for 20 hours at 25o C. Wash the organic solution with water, dilute aqueous sodium bicarbonate solution and with water. Dry the organic solution over a suitable dessicant, filter, and evaporate dichloromethane and any excess triethylamine. Crystallize the residue, 7-acetyl-10-(3-chlorophenyl)-6,8,9,10-tetrahydropyrido[2,3-b] [1,6]naphthyridin-5 (7H)-one, m.p. 238o-242o C. after recrystallization from CH3CN. Alternatively, the residue may be triturated with ether, and the solid collected on a filter and then crystallized.

By employing the 2-arylaminopyridinyl-3-carboxyl chloride and enamine listed in Columns 1 and 2 of Table 6 below, the compounds listed in Column 3 thereof are prepared by basically the same procedure. If the enamine bears a methylthio group on the same carbon attached to the enamine nitrogen atom, pass nitrogen gas through the resulting solution to remove liberated methane thiol. TABLE 6 [See Original Patent for Chemical Structure Diagram]

By employing the 2-arylaminopyridinyl-3-carboxylic chlorides and enamines listed in Columns 1 and 2 of Table 7 below, the products listed in Column 3 thereof may be prepared. TABLE 7 [See Original Patent for Chemical Structure Diagram]

EXAMPLE 6

With some compounds, the process of Example 5 may result in incomplete cyclization, i.e., intermediates of formula Ib or mixtures of such intermediates with the desired cyclized product may be produced. In such instances, the intramolecular cyclization of the intermediate to the desired product may be carried out by the following process.

The procedure of Example 4 above is repeated, except that the 2-(3-chlorophenylamino)-pyridinyl-3-carboxylic chloride and 2-(1-pyrrolidino)-indene are employed as the 2-arylaminopyridinyl-3-carbonyl chloride and enamine respectively. The intermediate product of the reaction, i.e., [2-(3-chlorophenylamino)-pyridinyl] [2-(1-pyrrolidino]-1-indenyl]methanone, (or mixture with the corresponding cyclized product) is treated with paratoluenesulfonic acid basically as described in Example 1 above (but substituting the intermediate (or mixture) for the primary amine and the enaminoketone) to produce 11-(3-chlorophenyl)-10,11-dihydro-5H-indeno[2,1-b] [1,8]naphthyridin-5-one, m.p. 304o-307o C. (d) after crystallization from C2H5OH.

EXAMPLE 7

Dissolve ethyl chloroformate (0.01 mole) in CH2Cl2 (40 ml). Add the resulting

solution over 30 min. to a 3o C.-solution of 2-anilinonicotinic acid (0.01 mole) and triethylamine (0.01 mole) dissolved in CH2Cl2 (400 ml). Keep the resulting solution at 3o C. for 2 hrs. to provide a solution containing 2-anilino-3-ethoxycarbonyloxycarbonyl-pyridine. Add a solution of the enamine 3,3-dimethyl-9-(1-pyrrolidinyl)-1,5-dioxaspiro[5.5]undec-8-ene (0.01 mole) dissolved in CH2Cl2 (60 ml) over 15 min. When the last addition is complete, keep the reaction mixture at 3o C. for another 2 hrs and at 25o C. for 24 hrs. Wash the CH2Cl2 solution with aqueous NaHCO3 solution, with water, with four portions of dilute aqueous HCl solution, and finally with water. After drying the CH2Cl2 solution, evaporate solvent to obtain the naphthyridinone, 6,8,9,10-tetrahydro-5',5'-dimethyl-10-phenyl-spiro[benzo-[b][1,8]naphthyridin-7-(5H), 2,[1,3]dioxan]-5-one, which is chromatographed as needed and is finally crystallized from ethyl acetate/methanol, m.p. 235.5o-238.5o C.

1-acetyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine can be employed as the enamine to produce 7-acetyl-6,8,9,10-tetrahydro-10-phenylpyrido[2,3-b][1,6]naphthyridin-5(7H)-one, m.p. 209.5o-212.5o, after crystallization from CH3CN.

U.S. Reissue Pat. No. 26,655 describes the commercially available (Aldrich Chemical Co.) 2-anilinonicotinic acid. The pyrrolidine enamine of 1,4-cyclohexanedione mono-2,2-dimethyltrimethylene ketal is known (Synth. Comm. 7, 417 (1977)), and the pyrrolidine enamine of 4-acetyl-1-piperidone is made according to J. Am. Chem. Soc. 76, 2029 (1954).

EXAMPLE 8

Dilute a 1M solution (73 ml) of lithium bistrimethylsilylamide in hexane with dry THF (75 ml), and add a solution of cyclopentanone (0.070 m) in THF. After brief stirring at 25o C., add a solution of methyl 2-phenylaminonicotinate (0.073 mol) in THF (48 ml). Reflux the solution for 22 hours, monitoring progress of the condensation by thin-layer chromatography.

When condensation is complete, cool the reaction mixture, evaporate solvent, and dissolve the residue in CHCl3. Wash the CHCl3 solution with water and with saturated aqueous NaCl solution. After drying the CHCl3 solution, evaporate the solvent to obtain the crude naphthyridinone. Purify the crude product by chromatography on silica gel with CHCl3, and crystallization from CH3CN to provide 6,7,8,9-tetrahydro-9-phenyl-5H-cyclopenta[b][1,8]-naphthyridin-5-one.

By employing the ketones and arylaminonicotinates indicated in Columns 1 and 2 of Table 8 below in basically the same process, the compounds listed in Column 3 are prepared. In these reactions THF or toluene are employed as solvents and lithum bistrimethylsilylamide, sodium hydride or freshly prepared sodium amide are employed as the base. TABLE 8

[See table in original]

EXAMPLE 9

With some compounds, the process of Example 8 results in incomplete cyclization to the desired naphthyridinone, i.e., a 1,3-diketone (or a mixture thereof with the desired cyclized product) results (see formula Ia above). In such instances, the intramolecular cyclization to the naphythyridinone may be

accomplished by subjecting the 1,3-diketone (or mixture) which results from the process of Example 8 to the following procedure.

For example, with 3,4-dihydro-6-methoxy-1-naphthalenone as the ketone and methyl 2-phenylaminonicotinate as the arylaminonicotinate, the 1,3-diketone, 3,4-dihydro-6-methoxy-2-[[2-(phenylamino)-3-pyridinyl]carbonyl]-1(2H)-napthalenone, results from the process of Example 8. To cyclize, reflux 9 g of the diketone in 400 ml of toluene containing a catalytic amount of p-toluenesulfonic acid. Collect the evolved water in a Dean-Stark trap. Remove the heat after 2 1/2 hours and allow the mixture to stand overnight. Distill the toluene under vacuum on a steam bath and crystallize the residue from acetonitrile, to provide the product 5,6-dihydro-3-methoxy-12-phenylnaphtho[1,2-b] [1,8]naphthyridin-7(12H)-one, m.p. 234o-237.5o C., after crystallization from CH3CN.

By employing basically the same procedure and employing the ketones and arylaminonicotinates listed in Columns 1 and 2 of Table 9 below, the compounds listed in Column 3 are prepared. TABLE 9 [See Original Patent for Chemical Structure Diagram]

EXAMPLE 10

The compound 3,4-dihydro-6-methoxy-2-[[2-(phenylamino)-3-pyridinyl]carbonyl]-1(2H)-naphthalenone, may be cyclized and dealkylated by heating 10 g of the diketone in 160 ml 48% hydrobromic acid on a steam bath with stirring for 48 hours. Remove the steam bath and stir for an additional 48 hours at ambient temperature. Pour the reaction mixture into ice water and basify with 50% sodium hydroxide solution while stirring. Collect the yellow precipitate by filtration and wash with ether. Stir the solid product in 200 ml of water and acidify the solution with glacial acetic acid. Collect the precipitated solid by filtration and wash with dilute acetic acid and then with water. Recrystallize the product 5,6-dihydro-3-hydroxy-12-phenylnaphtho[1,2-b] [1,8]naphthyridin-7(12H)-one from DMF, m.p. > 340o C.

Basically the same procedure is used with 3,4-dihydro-7-methoxy-2-[[2-(phenylamino)-3-pyridinyl]carbonyl]-1(2H)-naphthalenone to make 5,6-dihydro-4-hydroxy-12-phenyl-naphtho[1,2-b] [1,8]naphthyridin-7(12H)-one, m.p. > 330o, after crystallization from C2H5OH.

EXAMPLE 11

Oxidize 10-(3-chlorophenyl)-6,7,8,9-tetrahydropyrido[2,3-b] [1,6]naphthyridin-5(10H)-one with sodium tungstate and hydrogen peroxide, following the procedure of Chem. Commun. 874-875 (1984), to provide a mixture of a nitrone and a pyridine N-oxide which are separated by column chromatography on silica gel, each compound being eluted from the column by dichloromethane containing 2% methanol. The two compounds are 10-(3-chlorophenyl)-8,9-dihydro-pyrido[2,3-b] [1,6]naphthyridin-5(10H)-one-7-oxide, hemihydrate (m.p. 208o-209o C. after crystallization from CH3CN) and 10-(3-chlorophenyl)pyrido[2,3-b] [1,6]-naphthyridin-5(10H)-one-7-oxide m.p. 262o-265o C. after crystallization from CHCl3/CH3COOC2H5.

EXAMPLE 12

Reflux 10-(3-chlorophenyl)-8,9-dihydropyrido[2,3-b][1,6]naphthyridin-5(10H)-one-7-oxide (7.3 mmol), N-phenylmaleimide (7.4 mmol) in a solvent of ethylacetate (100 ml) and benzene (50 ml) for 15 hrs. Evaporate the solvents after filtration, and elute the residue from silca gel with chloroform. Crystallize the product, 8-(3-chlorophenyl)-6,7,13b,13c-tetrahydro-2-phenylpyrrolo[3",4":4',5']isoxazolo[2',3':1,2]pyrido[4,3-b][1,8]naphthyridin-1,3,13(2H,3aH,8H)-trione, from diisopropylether/CH3CN, m.p. 255o-258o C.

By employing the same nitrone and the compounds listed in Column 1 of Table 10 in place of N-phenylmaleimide in basically the same procedure, the compounds as listed in Column 2 of Table 10 are prepared. TABLE 10 [See Original Patent for Chemical Structure Diagram]

By basically the same procedure as described above employing the same nitrone and the compound listed in Column 1 of Table 11 below in place of phenylmaleimide, the compounds listed in Column 2 of Table 11 may be prepared, except that the last listed compound may be prepared by the procedure described in J. Org. Chem. 46, 3502 (1981). TABLE 11 [See Original Patent for Chemical Structure Diagram]

EXAMPLE 13

Charge a Paar bottle with 5,6-dihydro-3-hydroxy-12-phenyl-naphtho[1,2-b][1,8]naphthyridin-7(12H)-one, an equal weight of 5% Pd on carbon, and ethanol. Pressurize the bottle with hydrogen to about 50 psi, and shake the contents in a Paar apparatus at 25o C. Monitor the progress of hydrogenation by pressure changes or by thin-layer chromatography. When hydrogen uptake ceases, remove catalyst by filtration and ethanol by evaporation. Crystallize the residue to obtain 5,6,8,9,10,11-hexahydro-3-hydroxy-12-phenyl-naphtho[1,2-b][1,8]naphthyridin-7(12H)-one, m.p. > 330o C. after crystallization from C2H5OH.

By starting with the compounds listed in Column 1 of Table 12, the compounds listed in Column 2 thereof are prepared by basically the same procedure: TABLE 12 [See Original Patent for Chemical Structure Diagram]

EXAMPLE 14

Oxidize 6,7,8,9-tetrahydro-9-(3-methylthiophenyl)-5H-cyclopenta[b][1,8]naphthyridin-5-one with 3-chloroperbenzoic acid dissolved in CH2Cl2. Use one equivalent of peracid oxidant at 0o-5o C. for 5 hrs to make the corresponding sulfoxide, 6,7,8,9-tetrahydro-9-(3-methylsulfinylphenyl)-5H-cyclopenta[b][1,8]naphthyridin-5-one. Wash the reaction mixture with aqueous NaHCO3 solution and with water. After drying the CH2Cl2 solution, evaporate the solvent, and chromatograph the residue on silica gel. Elute the sulfoxide with CHCl3 containing increasing amounts of CH3OH and crystallize the product from CH3CN, m.p. 257o-259o C.

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By basically the same reaction but employing two equivalents of the peracid oxidant at 25o C. for 50 hrs., the corresponding sulfone, 6,7,8,9-tetrahydro-9-(3-methylsulfonylphenyl)-5H-cyclopenta[b][1,8]naphthyridin-5-one is prepared, m.p. 271o-273o, after crystallization from CH3CN. Similarly, starting with 10-(3-chlorophenyl)-6,8,9,10-tetrahydro-5H-thiopyrano[4,3-b][1,8]naphthyridin-5-one or 4-(3-chlorophenyl)-2,3,4,9-tetrahydrothieno[3,2-b][1,8]naphthyridin-9-one and one equivalent of the peracid oxidant, the sulfoxides, 10-(3-chlorophenyl)-6,8,9,10-tetrahydro-5H-thiopyrano[4,3-b][1,8]naphthyridin-5-one-7-oxide (m.p. 211o-212o C. after crystallization from CH3CN/CH3COOC2H5) or 4-(3-chlorophenyl)-2,3,4,9-tetrahydrothieno[3,2-b][1,8]naphthyridin-9-one-1-oxide (m.p. 266o-267o C. after crystallization form CH3CN), respectively, are prepared. By employing two equivalents of the peracid oxidant, the corresponding dioxides are prepared; i.e., 10-(3-chlorophenyl)-6,8,9,10-tetrahydro-5H-thiopyrano[4,3-b][1,8]naphthyridin-5-one-7,7-dioxide (m.p. 249o-250o C. after crystallization from CH3CN/pet. ether) and 4-(3-chlorophenyl)-2,3,4,9-tetrahydrothieno[3,2-b][1,8]naphthyridin-9-one-1,1-dioxide (m.p. 277o-278o C. after crystallization from CHCl3-CH3CN)..

EXAMPLE 15

Reflux 6,8,9,10-tetrahydro-5',5'-dimethyl-10-phenyl-spiro[benzo[b][1,8]naphthyridin-7-(5H),2'-[1,3]dioxan]-5-one (32 mmoles) with water (6 ml) and p-toluenesulfonic acid monohydrate (3.2 g) dissolved in 2-butanone (319 ml) for 3 days. Monitor the progress of hydrolysis by thin-layer chromatography. When hydrolysis is complete, cool the solution and evaporate the 2-butanone. Wash a CH2Cl2 solution of the residue with aqueous NaHCO3 solution and with water. Evaporate the CH2Cl2 after drying the organic solution, and crystallize the residue from C2H5OH-CHCl3 to obtain 6,8,9,10-tetrahydro-10-phenyl-benzo[b][1,8]naphthyridin-5,7-dione, m.p. 244o-247o C. (d).

EXAMPLE 16

Treat 5,6,8,9,10,11-hexahydro-3-methoxy-12-phenyl-naphtho[1,2-b][1,8]naphthyridin-7(12H)-one (10 mmoles) with equimolar amounts of acetyl chloride and triethylamine dissolved in CH2Cl2 (10 ml) at 0o-25o C. for 3 days. Wash the resulting solution with aqueous NaHCO3 solution and with water, and dry the organic solution. Evaporate the CH2Cl2, and chromatograph the residue on silica gel. Elute the N-acetylated product with 2% MeOH in CHCl3, and crystallize it from isopropyl acetate/disopropyl ether to provide 11-acetyl-5,6,8,9,10,11-hexahydro-12-phenyl-naphtho[1,2-b][1,8]naphthyridin-7(12H)-one, m.p. 178.5o-182o C.

EXAMPLE 17

Reflux 7-acetyl-6,8,9,10-tetrahydro-10-phenylpyrido[2,3-b][1,6]naphthyridin-5(7H)-one (10.9 grams) with hot, dilute (10%) aqueous hydrochloric acid (240 ml) in 95% ethanol (129 ml) for 8 hrs. Cool the resulting solution and collect the hydrochloride salt by filtration. If desired, the corresponding free base can be prepared by treating the hydrochloride salt with 50% aqueous sodium hydroxide solution. Crystallize the product, 6,8,9,10-tetrahydro-10-phenylpyrido[2,3-b][1,6]naphthyridin-5(7H)-one, monohydrate hydrochloride, from CH3OH/C2H5OOCCH3, m.p. 277o-279.5o C.

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By employing 7-acetyl-10-(3-chlorophenyl)-6,8,9,10-tetrahydropyrido[2,3-b][1,6]naphthyridin-5(7H)-one as the acetamide (30 g) in a similar procedure, (using N HCl (445 ml) and 95% ethanol (225 ml) for 15 hours), the product, 6,8,9,10-tetrahydro-10-(3-chlorophenyl)pyrido[2,3-b][1,8]naphthyridin-5(7H)-one may be prepared, m.p. 212o-215o C. after crystallization from CH2Cl2/CH3COCH3.

EXAMPLE 18

Charge a stainless-steel bomb with 9-(3-dimethylaminophenyl)-6,7,8,9-tetrahydro-5H-cyclopenta[b][1,8]naphthyridin-5-one (2 g), and with methyl iodide (80 ml). Close the bomb and heat it in a 140o C. oil bath for 20 hrs. Cool the bomb and contents, filter the latter, and wash the collected solid with ether to provide the product, 9-(3-trimethylammonium)-6,7,8,9-tetrahydro-cyclopenta[b][1,8]naphthyridin-5-(5H)-one iodide salt, m.p. 235o-239o C., after crystallization from H2O.

By a similar method 10-(3-chlorophenyl)-6,7,8,9-tetrahydropyrido[2,3-b][1,6]naphthyridin-5(10H)-one may be quaternized, using methyl iodide or ethyl iodide, respectively, to yield the products, 10-(3-chlorophenyl)-6,7,8,9-tetrahydro-7,7-dimethyl-pyrido[2,3-b][1,6] naphthyridinium-5(10H)-one, iodide (m.p. 305o-308o C. after crystallization from CH3OH) or 10(3-chlorophenyl)-6,7,8,9-tetrahydro-7,7-diethylpyrido[4,3-b][1,8] naphthyridinium-(5(10H)-one iodide 1/4 hydrate (m.p. 256o-258o C. after crystallization from CH3OH-CHCl3), respectively.

EXAMPLE 19

React 10-(3-chlorophenyl)-6,7,8,9-tetrahydropyrido[2,3-b][1,6]naphthyridin-5(10H)-one (5 mmol) with benzylbromide (5.8 mmol) in acetone (40 ml) at 25o C. for 3 hours. Evaporate the acetone solvent, and elute the product from silica gel with chloroform to provide the product, 10-(3-chlorophenyl)-6,7,8,9-tetrahydro-7-N-benzyl-pyrido[2,3-b][1,6]naphthyridin-5(10H)-one, m.p. 157o-161o C. after crystallization from CH3CN.

EXAMPLE 20

Oxidize 10-(3-chlorophenyl)-6,7,8,9-tetrahydropyrido[2,3-b][1,6]naphthyridin-5(10H)-one (1.6 mmol) in a refluxing solution of xylene (15 ml), using air as the oxidant and 5% Pd on C (15 mg) as the catalyst. Follow the procedure of Tetrahedron Letters 26, 1259-1260 (1985); pass air through the hot solution for 15 hours. Evaporate the xylene and elute the residue from silica gel with chloroform to provide 10-(3-chlorophenyl)pyrido[2,3-b][1,6]naphthyridin-5(10H)-one, m.p. 222o-224o C. after crystallization from CH3Cl/pet. ether.

EXAMPLE 21

Saponify 7-ethoxycarbonyl-10-(3-chlorophenyl)-6,7,8,9-tetrahydrobenzo[b][1,8]naphthyridin-5(10H)-one (7.1 g) with potassium hydroxide (1.10 g) in a solvent of ethanol and water (142 ml, 9:1 by volume). After 21 hours at 25o C., add water (200 ml), cool the resulting solution in ice, and acidify (pH 2) the solution with concentrated hydrochloric acid. Collect the resulting precipitate on a filter, and crystallize it from ethanol to provide

7-carboxy-10-(3-chlorophenyl)-6,7,8,9-tetrahydrobenzo[b] [1,8]naphthyridin-5(10H) -one, m.p. 279o-280.5o C.

EXAMPLE 22

Reduce 6,8,9,10-tetrahydro-10-phenylbenzo[b] [1,8]naphthyridin-5,7-dione (2 mmol) with sodium borohydride (50 mg) in a solvent of ethanol (30 ml) and water (0.25 ml). After 15 minutes, pour the reaction mixture over ice and collect the resulting precipitate on a filter. Reserve the precipitate, and extract the aqueous filtrate with chloroform. Dry the extracts, evaporate the chloroform, and combine the residue with the reserved precipitate to give the product, 10-phenyl-7-hydroxy-6,7,8,9-tetrahydro-benzo[b] [1,8]naphthyridin-5(10H)-one, m.p. 283o-286o C. after crystallization from ethanol.

EXAMPLE 23

Reduce the nitro group of 6,7,8,9-tetrahydro-9-(3-nitrophenyl)-5H-cyclopenta[b] [1,8]naphthyridin-5-one with stannous chloride in hydrochloric acid following the procedure of Org. Syn. (Coll. Vol. III, 1955, p. 453), precipitating the product, 9-(3-aminophenyl)-6,7,8,9-tetrahydrocyclopenta[b] [1,8]naphthyridin-5(5H)-one from H2O, m.p. 284.5o-285.5o C.

EXAMPLE 24

Reflux a mixture of 4-(3-chlorophenyl)-2,3-dihydrothieno[3,2-b] [1,8]naphthyridin-9(9H)-one (0.11 g), ethanol (100 ml), and commercial aged Raney nickel (from 5 ml of an aqueous suspension) for 10 hours under nitrogen. Filter the resulting mixture, evaporate the solvent, and chromatograph the residue over silica gel. Elute with CHCl3 to give 4-(3-chlorophenyl)-thieno[3,2-b] [1,8]naphthyridin-9(4H)-one, m.p. 264o-267o C. from CHCl3 hexane.

EXAMPLE 25

Add a solution containing a mixture of 1-acetyl-3-(1-pyrrolidinyl)-3-and 2-pyrrolines (3.55 g) and triethylamine (2.17 g) in dichloromethane (20 ml) to a cooled, stirred suspension of 2-(3-chlorophenylamino)pyridinyl-3-carbonyl chloride (5.26 g) in an atmosphere of N2. Use an ice bath for cooling. When addition is complete (30 minutes), remove the ice bath and allow stirring to continue at ambient temperature for 20 hours. Wash the resulting solution with 1M NaHCO3 solution, with H2O, with 1M HCl and with H2O. Dry the CH2Cl2 solution, filter it, and evaporate the CH2Cl2. Crystallize the residue to give 7-acetyl-9-(3-chlorophenyl)-6,7,8,9-tetrahydro-5H-pyrrolo[3,4-b] [1,8] naphthyridin-5-one, m.p. 289o-293o C. from CHCl3-C2H5OOCCH3. Chromatograph the mother liquor over silica gel, and elute the column with 2% CH3OH in CH2Cl2 to obtain 1-acetyl-2-[2-[(3-chlorophenyl)amino]-3-pyridinylcarbonyl]-3-(1-pyrrolidinyl)-1H -pyrrole, m.p. 170o-173o C. from CH3CN.

Reflux a mixture of 1-acetyl-2-[2-[(3-chlorophenyl)amino]-3-pyridinylcarbonyl]-3-(1-pyrrolidinyl)-1H -pyrrole (0.45 g), p-toluenesulfonic acid monohydrate (0.21 g) in a solvent of benzene (20 ml), and tert-butanol for 12 hours. Evaporate solvent and partition the residue between CHCl3 and 1M NaHCO3. Wash the CHCl3 solution with water, dry and filter the solution. Evaporate the solvent, and triturate the residue with CHCl3 to give 4-(3-chlorophenyl)-1,4-dihydro-9H-pyrrolo[3,2-b] [1,8]naphthyridin-9-one, m.p.

300o-301o C.

The following formulations exemplify some of the dosage forms of the compositions of this invention. In each, the term "active compound" designates 9-phenyl-6,7,8,9-tetrahydro-5H-cyclopenta[b][1,8]naphthyridin-5-one. It is contemplated, however, that this compound may be replaced by equally effective amounts of other compounds of formula I.

PHARMACEUTICAL DOSAGE FORM EXAMPLES

EXAMPLE A

Tablets

No.	Ingredient	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4 ") if needed. Dry the damp granules. Screen the dried granules if needed and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B

Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

EXAMPLE C

Parenteral

Ingredient	mg/vial	mg/vial
Active Compound Sterile Powder	100	500

Add sterile water for injection or bacteriostatic water for injection, for reconstitution.

EXAMPLE D

Injectable

Ingredient	mg/vial
Active Compound	100
Methyl p-hydroxybenzoate	1.8
Propyl p-hydroxybenzoate	0.2
Sodium Bisulfite	3.2
Disodium Edetate	0.1
Sodium Sulfate	2.6
Water for Injection q.s. ad	1.0 ml

Methods of Manufacture (for 1000 vials)

1. Dissolve p-hydroxybenzoate compounds in a portion (85% of the final volume) of the water for injection at 65o-70o C.

2. Cool to 25o-35o C. Charge an dissolve the sodium bisulfite, disodium edetate and sodium sulfate.

3. Charge and dissolve active compound.

4. Bring the solution to final volume by added water for injection.

5. Filter the solution through 0.22 membrane and fill into appropriate containers.

6. Finally sterilize the units by autoclaving.

EXAMPLE E

Nasal Spray

	mg/ml
Active Compound	10.0
Phenyl Mercuric Acetate	0.02
Aminoacetic Acid USP	3.7
Sorbitol Solution, USP	57.0
Benzalkonium Chloride Solution	0.2
Sodium Hydroxide 1N Solution to adjust pH	-
Water Purified USP to make	1.0 ml

The following formulations F and G exemplify some of topical dosage froms in which "Active Compound" refers to 9-(3-nitrophenyl)-6,7,8,9-tetrahydro-5H-cyclopenta[b][1,8]naphthyridin-5-one, but again other compounds of formula I may be substituted therefor.

EXAMPLE F

Ointment

Formula	mg/g

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Active Compound	1.0-20.0
Benzyl Alcohol, NF	20.0
Mineral Oil, USP	50.0
White Petrolatum, USP to make	1.0 g

Method of Manufacture

Disperse active compound in a portion of the mineral oil. Mix and heat to 65o C., a weighed quantity of white petrolatum, the remaining mineral oil and benzyl alcohol, and cool to 50o-55o C. with stirring. Add the dispersed active compound to the above mixture with stirring. Cool to room temperature.

EXAMPLE G

Cream

Formula	mg/g
Active Compound	1.0-20.0
Stearic Acid, USP	60.0
Glyceryl Monostearate	100.0
Propylene Glycol, USP	50.0
Polyethylene Sorbitan Monopalmitate	50.0
Sorbitol Solution, USP	30.0
Benzyl Alcohol, NF	10.0
Purified Water, USP to make	1.0 g

Method of Manufacture

Heat the stearic acid, glyceryl monostearate and polyethylene sorbitan monopalmitate to 70o C. In a separate vessel, dissolve sorbital solution, benzyl alcohol, water, and half quantity of propylene glycol and heat to 70o C. Add the aqueous phase to oil phase with high speed stirring. Dissolve the active compound in remaining quantity of propylene glycol and add to the above emulsion when the temperature of emulsion is 37o-40o C. Mix uniformly with stirring and cool to room temperature.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

CLAIMS: We claim:

[*1] 1. A compound having the name:

5-(3-chlorophenyl)-5,6,7,8-tetrahydro-9H-cyclopenta-[5,6]pyrido[2,3-b]pyrazin-9-one;

5-(3,4-dichlorophenyl)-5,6,7,8,-tetrahydro-9H-cyclopenta[5,6]pyrido[2,3-b]pyrazin-9-one;

5,6,7,8-tetrahydro-5-(3-nitrophenyl)-9H-cyclopenta[5,6]pyrido[2,3-b]pyrazine-9-one; or

5,6,7,8-tetrahydro-5-phenyl-9H-cyclopenta[5,6]pyrido[2,3]pyrazin-9-one.

[*2] 2. A pharmaceutical composition which comprises a compound as defined in claim 1 in combination with a pharamaceutically acceptable carrier.

[*3] 3. A method for treating allergic reactions in a mammel in need of such treatment which comprises administering to said mammal an effective amount of a compound defined in claim 1.

[*4] 4. A method for treating inflammation in a mammal in need of such treatment which comprises administering to said mammal an effective amount of a compound defined in claim 1.

[*5] 5. A method for treating peptic ulcers in a mammal in need of such treatment which comprises administering to said mammal an effective amount of a compound defined in claim 1.

[*6] 6. A method for treating hypertension in a mammal in need of such treatment which comprises administering to said mammal an effective amount of a compound defined in claim 1.

[*7] 7. A method for treating hyperproliferative skin disease in a mammal which comprises administering to said mammal an effective amount of a compound defined in claim 1.

[*8] 8. A method for suppressing the immune response in a mammal in need of such treatment which comprises administering to said mammal an effective immunosuppressive amount of a compound defined in claim 1.

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LEVEL 1 - 2 OF 3 PATENTS

5,074,874

<=2> GET 1st DRAWING SHEET OF 1

Dec. 24, 1991

Suture devices particularly useful in endoscopic surgery

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REL-US-DATA:
Division of Ser. No. 534,495, Jun. 7, 1990 now patented 4,981,149 Which is a division of Ser. No. 353,913, May 16, 1989 now patented 4,932,962

INT-CL: [5] A61B 17#00

US-CL: 606#224; 606#139; 606#151

CL: 606

SEARCH-FLD: 606#224-227, 151, 139

REF-CITED:

U.S. PATENT DOCUMENTS

1,293,660	2/1919	* Armstrong	606#225
2,715,486	8/1955	* Marloff-Moghadam et al.	606#224
4,069,825	1/1978	* Akiyama	606#158
4,182,341	1/1980	* Perri	606#225
4,901,721	2/1990	* Hakki	606#224
4,950,285	8/1990	* Wilk	606#151

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ASST-EXMR: Jackson, Gary

LEGAL-REP: Epstein, Edell & Retzer

ABST:
Suture devices, primarily for use in endoscopic surgery, include a suture needle having a length of suture material attached thereto with a contractible loop or passage at the proximal end of the suture material to allow the suture needle to be passed therethrough, the loop or passage contracting to clamp or grip the suture material to function similar to a conventional tied suture knot.

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NO-OF-CLAIMS: 9
EXMPL-CLAIM: <=9> 1

NO-OF-FIGURES: 11

NO-DRWNG-PP: 1

PARCASE:

This is a divisional application of application Ser. No. 07/534,495, filed June 7, 1990, U.S. Pat. No. *4,981,149*, which is a divisional application of application Ser. No. 07/353,913 filed May 16, 1989 now U.S. Pat. No. *4,932,962*.

SUM:

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to surgical suture devices and, more particularly, to suture devices made of bioabsorbable materials particularly useful in endoscopic surgery and methods of suturing using such suture devices.

2. Discussion of the Prior Art

Suturing of bodily tissue is a time consuming part of most surgical procedures including both open surgery and endoscopic or closed surgery. By open surgery is meant surgery wherein the surgeon gains access to the surgical site via a relatively large incision, and by endoscopic surgery is meant surgery wherein the surgeon gains access to the surgical site via one or more portals through which endoscopes are introduced to view the surgical site and through which instruments, such as forceps, cutters, applicators and the like, are introduced to the surgical site. There are many common endoscopic surgical procedures, including arthroscopy, laparascopy (pelviscopy), gastroentroscopy and laryngobronchoscopy, for example. In the past, suturing has been accomplished with the use of a sharp metal suture needle attached to the end of a length of suture material, the suture needle being caused to penetrate and pass through the tissue pulling the suture material through the tissue. Once the suture material has been pulled through the tissue, the surgeon ties a knot in the suture material, the knotting procedure allowing the surgeon to adjust the tension on the suture material to accommodate the particular tissue being sutured and control approximation, occlusion, attachment or other conditions of the tissue. The ability to control tension is extremely important to the surgeon regardless of the type of surgical procedure being performed; however, knotting of the suture material is time consuming and tedious work, particularly in microsurgery and endoscopic surgery. That is, in microsurgery suturing is necessarily time consuming due to the small size of the suture needle and the suture material and the concomitant difficult manipulation required to pass the suture needle through the tissue and to tie a knot in the suture material. With respect to endoscopic surgery, suturing and tying knots represents an even more time consuming procedure due to the difficult maneuvers required. Accordingly, while endoscopic surgery would be preferred for most procedures, the advantages are often outweighed by the disadvantages caused by the length of time required to complete the endoscopic surgical procedure, which time is greatly extended

due to the time required for suturing. Another disadvantage of suturing with a metal suture needle and suture material during endoscopic surgery is that the suture needle is difficult to hold and manipulate and can be easily dropped. Should the suture needle be dropped, open surgery with its attendant disadvantages must be performed to find and remove the needle.

There have been many attempts to provide devices to take the place of conventional suturing with a suture needle and a length of suture material; however, such prior art devices have essentially been staples, clips, clamps or other fasteners not providing the adjustable tension obtained by the surgeon while knotting a length of suture material. U.S. Pat. Nos. *3,827,277* to Weston, 4,060,089 to Noiles, 4,490,326 to Beroff et al, 4,513,746 to Aranyi et al, 4,532,926 to O'Holla, 4,548,202 to Duncan, 4,573,469 to Golden, No. 4,590,937 to Deniega, 4,595,007 to Meride, 4,602,634 to Barkley, 4,646,741 to Smith, 4,671,280 to Dorband et al, 4,719,917 to Barrows et al and 4,741,337 to Smith et al are representative of such prior art devices for use in place of conventional suturing. Many of these prior art devices are made of bioabsorbable materials such that the devices are absorbed over time into the bodily tissue and do not have to be removed after the bodily tissue has healed.

There exist many compositions useful as bioabsorbable materials, as represented by the above patents and by U.S. Pat. Nos. *3,739,773* to Schmitt et al, 3,797,499 to Schneider, 4,141,087 to Shalaby et al, 4,300,565, 4,523,591 to Kaplan et al and 4,649,921 to Koelmel et al which discuss characteristics of various bioabsorbable materials and medical devices desirably manufactured of such materials, such medical devices being of a type designed to be engaged in, embedded in or otherwise attached to various types of bodily tissue, such as bone, muscle, organs, skin and other soft tissue, to remain in place in the tissue until the device is absorbed into the body.

U.S. Pat. No. *3,570,497* to Lemole discloses a suture device formed of a needle with a piercing point extending from a latch cord carrying notches designed to pass through a latch collar, the latch cord being resilient to be curved upon itself to form a suture stitch without requiring tying of a knot; however, the latching function does not provide the same feel and tension control as knotting a length of suture material. U.S. Pat. No. *4,548,202* to Duncan uses similar structure in a tissue fastener device in that serrations or angled barbs are provided on spaced legs passing through tissue to be engaged by an apertured receiver or a flexible filament mesh. U.S. Pat. No. *3,123,077* to Alcamo discloses a surgical suture carrying raised projections or depressions or teeth such as barbs or spicules to snag or penetrate tissue to effectively hold a sewed incision or wound.

Endoscopic surgery is preferred over open surgery due to the greatly reduced trauma and wound healing time for the patient and due to concomitant cost savings associated with shorter hospital stays and performing surgery without general anesthesia and in non-hospital or out-patient surgery sites. Accordingly, there has been much effort spent to develop techniques for facilitating the suturing normally performed by use of a metal suture needle and a length of suture material. Alternative techniques proposed have included electrical coagulation, mechanical devices such as clips, clamps and staples, and lasers; however, no well accepted alternative has yet been found in that suturing and tying are essential and vital parts of most surgical procedures. That is, to date the proposed alternatives have had disadvantages, including

increased risk to the patient, while not providing the surgeon with the advantages of suturing and tying and not being useful in a wide range of procedures to allow expansion of the areas in which endoscopic surgery can be effectively performed. Thus, there is a great need for suture devices, particularly useful in endoscopic surgery, that allow surgeons to suture and tie knots in a manner with which they are familiar without undue concern as to the loss of the suture needle and further for suture devices that allow controlled approximation of tissue and tying to produce controlled tension.

SUMMARY OF THE INVENTION

Accordingly, it is a primary object of the present invention to provide suture devices particulary useful in endoscopic surgery overcoming the above mentioned disadvantages of the prior art.

Another object of the present invention is to construct a suture needle of the type attached to a length of suture material to pull the suture material through tissue to be sutured of a bioabsorbable material such that, should the suture needle be dropped or lost during endoscopic surgery, open surgery is not required to remove the needle.

A further object of the present invention is to facilitate attachment of a length of suture material to a suture needle made of bioabsorbable material by using the plastic characteristics of the bioabsorbable material.

An additional object of the present invention is to form a loop or passage in the proximal portion of a length of suture material in a manner such that the loop or passage tightly grips the length of suture material after a suture needle attached to the distal end of the length of suture material has passed through the loop or passage to pull the length of suture material therethrough forming an adjustably controlled knot after suturing.

The present invention has another object in that a suture needle is formed of bioabsorbable material with a rigid distal portion having a sharp tip and semi-rigid or flexible proximal and/or central portions to facilitate manipulation of the suture needle for various procedures.

Yet an additional object of the present invention is to provide a suture needle that can be used to position a length of suture material in tissue to be sutured and can be left embedded in the tissue by constructing the suture needle of bioabsorbable material.

The present invention is generally characterized in a suture device for joining bodily tissue formed of a length of suture material and a suture needle having a distal end with a sharp penetrating point and a proximal end with means for engaging the length of suture material such that the suture needle can penetrate tissue to be sutured to pull the length of suture material through the tissue to leave the length of suture material in the tissue, the suture needle being made of bioabsorbable material whereby said suture needle can be absorbed by the body.

Some of the advantages of the present invention over the prior art are that open surgery is not required should a suture needle be dropped or lost during endoscopic surgery, suture needles can be made with controlled rigidity to facilitate specific surgical procedures, attachment of the suture needle to a

length of suture material is facilitated by the plastic characteristics of the bioabsorbable material, and a knotting or suture tying function is provided by passing a suture needle through a contractible passage or loop carried at a proximal portion of a length of suture material attached to the suture needle.

Other objects and advantages of the present invention will become apparent from the following description of the preferred embodiments taken in conjunction with the accompanying drawings.

DRWDESC:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a side view of a suture device formed of a suture needle and a length of suture material in accordance with the present invention.

FIG. 2 is a broken sectional view of the suture device of FIG. 1.

FIG. 3 is an exploded perspective view showing formation of the suture device of FIG. 1.

FIGS. 4 and 5 are broken sectional views of modifications of the suture device of FIG. 1.

FIG. 6 is an exploded side view of another embodiment of a suture device according to the present invention.

FIG. 7 is a side view of the assembled suture device of FIG. 6.

FIG. 8 is a perspective view of another embodiment of a suture device according to the present invention.

FIG. 9 is a broken side view illustrating use of the suture device of FIG. 8.

FIG. 10 is a perspective view of another embodiment of a suture device according to the present invention.

FIG. 11 is a section taken along line 11-11 of FIG. 10.

DETDESC:

DESCRIPTION OF THE PREFERRED EMBODIMENTS

A suture device 30 according to the present invention is illustrated in FIGS. 1 and 2 and is formed of a suture needle 32 having a curved, C-configuration as shown in FIG. 1 or straight or slightly curved shapes as shown in FIGS. 4 and 5 at 32a and 32b, respectively, or any other conventional suture needle shape, the suture device 30 also including a length of suture material 34 attached or secured to a proximal end 36 of the suture needle. By suture needle is meant a needle specifically designed for penetrating bodily tissue and pulling through the tissue a length of suture material to approximate edges of tissue, such as result from an incision or wound, to permit the tissue to join together during healing. Suture needles are severed from the suture material once the suturing procedure of placing sufficient stitches or loops of suture material in the tissue is completed and are commonly made of metal. That is, suture needles are not designed to remain in the tissue but rather serve only the purpose of

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penetrating the tissue to position the suture material therein. After the suturing procedure and severing of the suture needles, the suture needles are conventionally sterilized for reuse or, more commonly, discarded.

In accordance with the present invention, the suture needle 32 is made of bioabsorbable material even though suture needles are not intended to remain in the tissue as are medical devices commonly made of bioabsorbable material. The bioabsorbable material is rigid at a sharp point 38 on a distal portion of the suture needle to easily penetrate tissue to be sutured and can be rigid throughout the length thereof, or a proximal portion adjacent proximal end 36 can also be rigid while a central portion extending between the distal and proximal portions can be flexible to facilitate particular suturing maneuvers. In addition, both the central and proximal portions can be flexible for use in other suturing maneuvers, it being appreciated that the ability to make certain portions of the needle flexible provides many advantages in endoscopic surgery due to the limitations concomitant with suturing in a confined area with the use of a needle holder. The length of suture material 34 is preferably also made of bioabsorbable material but could be made of conventional materials, the suture material being flexible to conform to the desired suturing configuration in the tissue. For some uses, it is preferable for the suture material to be made of a flexible, elastic (stretchable) bioabsorbable material. The suture material 34 preferably has a diameter the same as the width or diameter of the proximal end 36 of the suture needle and has an end 35 extending from a distal portion and having a reduced diameter to be received in the bore 39 in a manner to produce a smooth profile to facilitate suturing. As shown in FIG. 3, a preferred manner of forming the suture device 30 is by molding the suture needle 32 with the end of the suture material 34 positioned in the mold such that the suture needle is formed simultaneously with attachment of the suture material. The mold has two parts 40 and 42 with recesses 44 and 46 therein having the shape of suture needle 32, and an inlet channel 48 is provided for injection of a bioabsorbable material under pressure. Channels 50 and 52 are formed in mold parts 40 and 42 to accommodate suture material 34 and are essentially extensions of recesses 44 and 46 such that, during injection molding of the suture needle 32, the end of the suture material 34 is captured and securely attached to the proximal end 36 of the suture needle. The end of the suture material can extend as far into the molding recesses as required to produce a secure attachment. In forming the suture needle 32, the plastic characteristics of the bioabsorbable material can be used to great advantage by controlling the flexibility or rigidity of the suture needle to facilitate use in particular surgical procedures. To this end, channels 48a and 48b can be positioned in mold parts 40 and 42 such that bioabsorbable materials with varying characteristics can be injected to create a suture needle having a specifically designed flexibility profile. For example, the portion adjacent sharp needle point 38 is preferably rigid, that is the portion distally of channel 48b, while a central portion between channels 48a and 48b can be flexible or rigid while the proximal portion between channels 48a and 48 can be flexible or rigid.

While it is preferred to mold the suture needle simultaneously with attaching the suture material since manufacture of the suture device is facilitated and made less expensive by accomplishing two manufacturing processes in a single step, the end of the suture material can also be attached to the proximal end 36 by various mechanical means such as by threading the bore 39a and the end 35a, as shown in FIG. 4, or providing a spherical recess 39b in proximal end 36b which is slit to expand to receive a ball-shaped end 35b on suture material 34b having two lengths as shown in FIG. 5. Additionally, the end of the suture

material can be secured to the suture needle with the use of adhesives and/or heat treating or ultrasonic welding. Since the suture needle is made of bioabsorbable material, bore 39 can have any length desired thereby allowing more secure attachment of the suture material thereto. The suture material could also be secured in the bore of the suture needle by anchoring or staking; however, it is preferable to take advantage of the plastic characteristics of the bioabsorbable material of the suture needle as well as the plastic characteristics of the suture material, when made of bioabsorbable material, in that the end of the suture material can be formed in any suitable manner with protrusions to be received in the bore or recess in the proximal end of the suture needle with the latter having a configuration to lock the end therein.

The suture device 30 is used in a manner similar to conventional suturing, it being appreciated that, when used in endoscopic procedures, the suture needle 32 will be held by a conventional needle holder to cause the suture needle to penetrate through the tissue in a manner to thread the suture material in the tissue to approximate the edges of the tissue as desired. The suture needle 32 is severed from the suture material 34 after the suturing procedure is completed; and, should the suture needle be dropped and lost prior to removal through the portal, open surgery is not required to find and remove the suture needle since it is made of bioabsorbable material and can be absorbed by the body. Accordingly, the suture needle 32 can be left in the body after suturing due to inadvertence. Furthermore, since the suture needle is made of bioabsorbable material, the suture needle can be intentionally lodged in the tissue after suturing to additionally approximate and hold the tissue together. Accordingly, by making the suture needle of bioabsorbable material many unexpected advantages are obtained including facilitating manufacture of the suture needle to particular specifications as to rigidity and configuration, facilitating attachment of a length of suture material thereto, allowing endoscopic procedures to be performed with less apprehension relating to inadvertent loss of the suture needle and allowing the suture needle to be used to additionally secure the tissue.

Another embodiment of a suture device according to the present invention is illustrated in FIGS. 6 and 7 wherein a suture device 52 is formed of a suture needle 54 and a length of suture material 56 preferably made of flexible bioabsorbable material. The suture needle 54 is formed of bioabsorbable material to have a desired rigidity therealong as described above; and, while a straight configuration is illustrated, the suture needle can have any desired configuration corresponding to commonly used suture needles such as the configurations shown in FIGS. 1, 4 and 5. The suture needle 54 has a hollow proximal end 58 forming a bore or recess 60 therein, and angled perforations or holes 62 extend through the wall surrounding the bore. The end of the suture material 56 has angled, whisker-like filaments 64 extending rearwardly therefrom having a size to be received in the holes 62 in the suture needle, the holes 62 similarly extending rearwardly from the inner surface to the outer surface toward the proximal end of the suture needle. To secure the suture material 56 to the suture needle 54, the end of the suture material is simply forced into the recess 60 until the end of the recess is reached; and, thereafter, the suture material is pulled rearwardly or away from the suture needle causing the whisker-like filaments 64 to pass through the holes 62 providing a secure attachment. As shown in FIG. 7, the whisker-like filaments 64 may extend beyond the outer surface of the suture needle; however, the whiskers are angled proximally away from the sharp tip at the distal end of the suture needle

thereby not interfering with smooth suturing. Of course, the filaments 64 can have a length less than the length of the holes 62 so as not to extend externally of the suture needle. The suture device 52 is used in a similar fashion as the suture device 30.

The bore or recess 60 can extend along the length of the suture needle 54 as shown at 61 in dashed lines to form a lumen or chamber such that various local and/or systematic drugs can be stored in the lumens to be dispensed via the holes to the suture site. Such drugs include, for example, insulin, antitumor agents, antibiotics, contraceptive agents and the like. That is, by making the suture needles hollow with holes extending through the walls communicating with the lumen or chamber, drugs can be efficaciously applied to the suture site during suturing, and the lumen or chamber can be filled with a drug to be dispensed via the opening in the proximal end 58 and sealed in the suture needle by attachment of the suture material which does not extend the length of the lumen.

Another embodiment of a suture device according to the present invention is illustrated in FIG. 8 wherein a suture device 66 is formed of a suture needle 68 made of bioabsorbable material to have a desired rigidity therealong as described above and having any desired curved or straight configuration commonly used for suture needles with an eye 70 formed in a proximal end 72 thereof. A length of suture material 74, preferably made of flexible, elastic or stretchable bioabsorbable material, is attached to the suture needle 68 by passing the suture material through the eye 70, folding it back upon itself, slipping a ring or ring-like member 76, preferably made of bioabsorbable material, over the adjacent lengths of the suture material and securing the ends of the lengths of suture material together at an enlarged proximal end member 77, for example, by fusing or welding. The enlarged proximal end member 77 has a tapered locking neck 78 extending distally therefrom with protrusions thereon, such as proximally angled barbs, such that the locking neck can be received in the ring 76 in locking engagement.

In use, suturing is accomplished with the suture needle 68 in normal fashion with a double filament of the suture material pulled through the tissue, as shown in FIG. 9; and, the suture needle 68 is passed through a contractible loop or passage 79 defined by the adjacent lengths of suture material, the ring 76 and the enlarged proximal end member 77. Accordingly, the suture material 74 can be pulled tight until the ring 76 and the stretchable suture material proximal end member 77 abut the tissue with the desired tension, the neck 78 passing through the ring to lock the suture material in place and function similar to a conventional suture knot. After the suture material has been clamped between the proximal end member 77 and the ring 76 by the locking interaction therebetween, the suture material can be severed as shown at the dashed line C and the suture needle removed or the suture needle can be lodged in the tissue. If desired, an opening can be formed in the proximal end 72 of the suture needle to allow insertion of the length of suture material therein, and the suture material can be twisted to assure attachment of the suture material to the suture needle.

Another embodiment of a suture device according to the present invention is illustrated in FIGS. 10 and 11 wherein a suture device 80 is formed of a suture needle 81 made of bioabsorbable material to have a desired rigidity therealong as described above and having any desired curved or straight configuration commonly used for suture needles, the suture needle having a proximal end 82

formed with an arcuate channel 83 therein, circular in cross-section, extending from a side entrance 84 to an end position 86 aligned with the longitudinal axis of the suture needle. A mouth 88 communicates with the channel 83 to receive a reduced diameter projection 89 at the distal end of a length of suture material 90, preferably made of flexible, elastic or stretchable bioabsorbable material. A ball 92 is formed on the end of projection 89, and the length of suture material has a proximal end 94 formed of an elastic loop 96 that can be stretched open, as shown in dash lines to define a passage 98 therethrough. The suture material 90 is attached to the suture needle 81 by inserting the ball 92 in the enlarged opening of entrance 84 and moving the ball along channel 83 to the end position 86, the projection 89 passing through mouth 88. The suture device 80 is used in a manner similar to that described above with respect to suture device 66 in that, after the suture needle penetrates the tissue to pull the suture material through the tissue, suture needle 81 is passed through the passage 98 in the proximal end which stretches to accommodate the largest transverse dimension of the suture needle and, thus, acts like loop 79 allowing the suture material to be pulled tight until the proximal end abuts the tissue with desired tension on the suture material. That is, the loop 96 contracts to clamp the length of suture material in the manner of a conventional suture knot, and the suture needle 81 can either be removed or lodged in the tissue.

Various bioabsorbable or biodegradable materials can be used to make the suture devices of the present invention with the composition determined by the rigidity or flexibility required. Generally, the bioabsorbable materials are thermoplastic polymers such as absorbable polymers and copolymers of poly-dioxanne, lactide, glycolide and the like. Polyglycolic acid is disclosed in U.S. Pat. Nos. *3,463,158*; *3,739,773* and *3,772,420*. Suitable polylactic acids are disclosed in U.S. Pat. No. *3,636,956*. Examples of absorbable polyesters are shown in U.S. Pat. Nos. *3,225,766* and *3,883,901*. Absorbable cellulose glycolic acid ethers are shown in U.S. Pat. No. *2,764,159*. Examples of suitable esters of alpha-cyanoacrylic acid are found in U.S. Pat. Nos. *3,527,841*, *3,564,078* and *3,759,264*. The variable rigidity of the suture needles can be obtained by changing the bioabsorbable material composition in portions of the suture needles or by coating portions of the suture needles with bioabsorbable materials such as polycaprilactone.

The suture devices of the present invention can be any size from micro to macro dependent upon the surgical procedures for which they are designed for use; and, it should be appreciated that, while the suture devices of the present invention are particularly designed for use in endoscopic or closed procedures, they can also be used in open procedures since the time required for suturing is substantially reduced resulting in a significant reduction in overall operating time. The suture needles can taper throughout their length to a sharp tip or can have a constant diameter or cross section along their length with a sharp conical, pyramidal or polygonal tip at the distal end. The configuration of the suture needles in cross section can be varied in accordance with surgical procedures to be performed including, for example, circular, semi-circular, oval, lunar, rectangular, hexagonal, and polygonal solid or hollow configurations. Additionally, the outer surfaces of the suture needles can be grooved to facilitate penetration. The suture needles can be made in any conventional manner of working with plastic materials including molding, extrusion, stamping or cutting, and the suture needles and suture materials can be formed simultaneously or separately.

The lengths of suture materials can be made of conventional non-bioabsorbable materials or of bioabsorbable materials and can be elastic or stretchable for specific surgical procedures. As shown in FIGS. 5 and 8, multiple lengths of suture materials can be attached to the suture materials for specific surgical procedures and to effect a knot tying function.

Inasmuch as the present invention is subject to many variations, modifications and changes in detail, the above description of the preferred embodiments is intended to be exemplary only and not limiting.

CLAIMS: What is claimed:

[*1] 1. A suture device for joining bodily tissue comprising

a suture needle having a sharp, tissue penetrating distal end and a proximal end; and

suture material means having distal means attached to said proximal end of said suture needle and proximal means including passage means for passage of said cuture needle therethrough, said passage means being contractible for clamping a portion of said suture material means therein after said suture needle has passed therethrough whereby said suture mateial means is controllably held in place in the tissue after suturing.

[*2] 2. A suture device as recited in claim 1 wherein said suture material means includes first and second lengths of suture material having proximal ends and said passage means includes an end member connected with said proximal ends of said first and second lengths of suture material and a ring-like member surrounding said first and second lengths of suture material and movable longitudinally therealong to define a loop for passage of said suture needle therethrough between said end member, said ring-like member and said first and second lengths of said suture material.

[*3] 3. A suture device as recited in claim 2 and further comprising means for locking said end member in engagement with said ring-like member.

[*4] 4. A suture device as recited in claim 3 wherein said suture material means is made of bioabsorbable material.

[*5] 5. A suture device as recited in claim 3 wherein said suture needle is made of bioabsorbable material.

[*6] 6. A suture device as recited in claim 1 wherein said passage means is made of a loop of elastic material stretchable for passage of said suture needle therethrough.

[*7] 7. A suture device as recited in claim 6 wherein said suture material means includes a single length of suture material having a distal end connected with said loop of elastic material.

[*8] 8. A suture device as recited in claim 7 wherein said suture material means is made of bioabsorbable material.

[*9] 9. A suture device as recited in claim 7 wherein said suture needle is made of bioabsorbable material.

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LEVEL 1 - 3 OF 3 PATENTS

5,053,047

<=2> GET 1st DRAWING SHEET OF 2

Oct. 1, 1991

Suture devices particularly useful in endoscopic surgery and methods of suturing

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US-CL: 606#223; 606#230; 606#232

CL: 606

SEARCH-FLD: 606#221, 224, 228, 232, 225, 216, 213, 223, 230

REF-CITED:

U.S. PATENT DOCUMENTS

2,413,142	12/1946	* Jones et al.	606#216
2,883,096	1/1957	* Dawson	
3,123,077	3/1964	* Alcamo	606#228
3,166,072	1/1965	* Sullivan, Jr.	606#221
3,206,086	7/1963	* Duffney	
3,233,800	2/1966	* Catania	606#225
3,412,912	10/1966	* Rosenberg	
3,570,497	3/1971	* Lemole	606#224
3,739,773	6/1973	* Schmitt et al.	
3,797,499	3/1974	* Schneider	
3,827,277	8/1974	* Weston	
4,006,747	2/1977	* Kronenthal	606#221
4,060,089	11/1977	* Noiles	
4,141,087	2/1979	* Shalaby et al.	
4,300,565	11/1981	* Rosensaft et al.	
4,429,080	1/1984	* Casey et al.	
4,490,326	12/1984	* Beroff	
4,510,934	4/1985	* Batra	
4,513,746	4/1985	* Aranyi et al.	
4,523,591	6/1985	* Kaplan et al.	
4,532,926	8/1985	* O'Holla	
4,548,202	10/1985	* Duncan	606#220
4,573,469	3/1986	* Golden et al.	
4,590,937	5/1986	* Deniega	
4,595,007	6/1986	* Mericle	
4,602,634	7/1986	* Barkley	

4,646,741	3/1987	* Smith	
4,649,921	3/1987	* Koelmel et al.	
4,671,280	6/1987	* Dorband et al.	
4,719,917	1/1988	* Barrows et al.	
4,741,337	5/1988	* Smith et al.	
4,744,365	5/1988	* Kaplan et al.	
4,832,026	5/1989	* Jones	606#335
4,873,976	10/1989	* Schreiber	

FOREIGN PATENT DOCUMENTS

213834	9/1984	* German Democratic Republic	
86/03396	6/1976	* World Intellectual Property Organization	128#339

PRIM-EXMR: Pellegrino, Stephen C.

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ABST:
Suture devices, particularly useful in endoscopic surgery, include a suture device made of bioabsorbable material having an elongate body member with a sharp distal end for penetrating tissue and means for locking the suture device in tissue to prevent forward and rearward movement and a suture device made of bioabsorbable material having a hinge-like joint for folding a distal portion at a precise location to be juxtaposed with a proximal portion for adjustable locking. Methods of using the suture devices for joining tissue sections, such as in tuboplasty, for closing anatomical lumens and for subcuticular suturing.

NO-OF-CLAIMS: 21

EXMPL-CLAIM: <=37> 1

NO-OF-FIGURES: 25

NO-DRWNG-PP: 2

SUM:

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to surgical suture devices and, more particularly, to suture needle-like suture devices made of bioabsorbable materials particularly useful in endoscopic surgery and methods of suturing using such suture devices.

2. Discussion of the Prior Art

Suturing of bodily tissue is a time consuming part of most surgical procedures including both open surgery and endoscopic or closed surgery. By open surgery is meant surgery wherein the surgeon gains access to the surgical site

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via a relatively large incision, and by endoscopic surgery is meant surgery wherein the surgeon gains access to the surgical site via one or more portals through which endoscopes are introduced to view the surgical site and through which instruments, such as forceps, cutters, applicators and the like, are introduced to the surgical site. There are many common endoscopic surgical procedures, including arthroscopy, laparascopy (pelviscopy), gastroentroscopy and laryngobronchoscopy, for example. In the past, suturing has been accomplished with the use of a sharp metal suture needle attached to the end of a length of suture material, the suture needle being caused to penetrate and pass through the tissue pulling the suture material through the tissue. Once the suture material has been pulled through the tissue, the surgeon ties a knot in the suture material, the knotting procedure allowing the surgeon to adjust the tension on the suture material to accommodate the particular tissue being sutured and control approximation, occlusion, attachment or other conditions of the tissue. The ability to control tension is extremely important to the surgeon regardless of the type of surgical procedure being performed; however, knotting of the suture material is time consuming and tedious work, particularly in microsurgery and endoscopic surgery. That is, in microsurgery suturing is necessarily time consuming due to the small size of the suture needle and the suture material and the concomitant difficult manipulation required to pass the suture needle through the tissue and to tie a knot in the suture material. With respect to endoscopic surgery, suturing and tying knots represents an even more time consuming procedure due to the difficult maneuvers required. Accordingly, while endoscopic surgery would be preferred for most procedures, the advantages are often outweighed by the disadvantages caused by the length of time required to complete the endoscopic surgical procedure, which time is greatly extended due to the time required for suturing. Another disadvantage of suturing with a metal suture needle and suture material during endoscopic surgery is that the suture needle is difficult to hold and manipulate and can be easily dropped. Should the suture needle be dropped, open surgery with its attendant disadvantages must be performed to find and remove the needle.

There have been many attempts to provide devices to take the place of conventional suturing with a suture needle and a length of suture material; however, such prior art devices have essentially been staples, clips, clamps or other fasteners not providing the adjustable tension obtained by the surgeon while knotting a length of suture material. U.S. Pat. Nos. *3,827,277* to Weston, No. 4,060,089 to Noiles, No. 4,490,326 to Beroff et al, No. 4,513,746 to Aranyi et al, No. 4,532,926 to O'Holla, No. 4,548,202 to Duncan, No. 4,573,469 to Golden, No. 4,590,937 to Deniega, No. 4,595,007 to Meride, No. 4,602,634 to Barkley, No. 4,646,741 to Smith, No. 4,671,280 to Dorband et al, No. 4,719,917 to Barrows et al and No. 4,741,337 to Smith et al are representative of such prior art devices for use in place of conventional suturing. Many of these prior art devices are made of bioabsorbable materials such that the devices are absorbed over time into the bodily tissue and do not have to be removed after the bodily tissue has healed.

There exist many compositions useful as bioabsorbable materials, as represented by the above patents and by U.S. Pat. Nos., 3,739,773 to Schmitt et al, No. 3,797,499 to Schneider, No. 4,141,087 to Shalaby et al, No. 4,300,565, No. 4,523,591 to Kaplan et al and No. 4,649,921 to Koelmel et al which discuss characteristics of various bioabsorbable materials and medical devices desirably manufactured of such materials, such medical devices being of a type designed to be engaged in, embedded in or otherwise attached to various types of bodily

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tissue, such as bone, muscle, organs, skin and other soft tissue, to remain in place in the tissue until the device is absorbed into the body.

U.S. Pat. No. *3,570,497* to Lemole discloses a suture device formed of a needle with a piercing point extending from a latch cord carrying notches designed to pass through a latch collar, the latch cord being resilient to be curved upon itself to form a suture stitch without requiring tying of a knot; however, the latching function does not provide the same feel and tension control as knotting a length of suture material. U.S. Pat. No. *4,548,202* to Duncan uses similar structure in a tissue fastener device in that serrations or angled barbs are provided on spaced legs passing through tissue to be engaged by an apertured receiver or a flexible filament mesh. U.S. Pat. No. *3,123,077* to Alcamo discloses a surgical suture carrying raised projections or depressions or teeth such as barbs or spicules to snag or penetrate tissue to effectively hold a sewed incision or wound.

Endoscopic surgery is preferred over open surgery due to the greatly reduced trauma and wound healing time for the patient and due to concomitant cost savings associated with shorter hospital stays and performing surgery without general anesthesia and in non-hospital or out-patient surgery sites. Accordingly, there has been much effort spent to develop techniques for facilitating the suturing normally performed by use of a metal suture needle and a length of suture material. Alternative techniques proposed have included electrical coagulation, mechanical devices such as clips, clamps and staples, and lasers; however, no well accepted alternative has yet been found in that suturing and tying are essential and vital parts of most surgical procedures. That is, to date the proposed alternatives have had disadvantages, including increased risk to the patient, while not providing the surgeon with the advantages of suturing and tying and not being useful in a wide range of procedures to allow expansion of the areas in which endoscopic surgery can be effectively performed. Thus, there is a great need for suture devices, particularly useful in endoscopic surgery, that allow surgeons to suture and tie knots in a manner with which they are familiar without undue concern as to the loss of the suture needle and further for suture devices that allow controlled approximation of tissue and tying to produce controlled tension.

SUMMARY OF THE INVENTION

Accordingly, it is a primary object of the present invention to provide suture devices particularly useful in endoscopic surgery overcoming the above mentioned disadvantages of the prior art.

Another primary object of the present invention is to construct a suture device having characteristics similar to a suture needle such that a surgeon can manipulate the suture device to penetrate tissue using techniques similar to those used for suturing with a suture needle and a length of suture material.

A further object of the present invention is to provide a suture needle-like suture device in the form of a body member made of bioabsorbable material having an enlarged proximal end, a sharp distal end and protrusions therebetween configured such that the suture device can be inserted through tissue in only a forward direction and locked in the tissue with forward movement limited by the enlarged proximal end and rearward movement limited by the protrusions which can be whisker-like filaments angled away from the sharp distal end toward the enlarged proximal end. Any portion of the distal end of the needle protruding

from the tissue can be cut off and removed.

An additional object of the present invention is to provide a suture needle-like suture device for joining bodily tissue having a distal portion terminating at a sharp tip and a proximal portion hingedly connected with the distal portion such that the distal portion can penetrate the tissue and be folded or bent at the hinge to a position juxtaposed with the proximal portion with the sharp tip received in an opening carried by the proximal portion to be adjustably locked therein.

Another object of the present invention is to provide a method of suturing an opening in skin by penetrating the subcutaneous fat layer with suture needle-like suture devices made of bioabsorbable material and movable only in a forward direction to approximate the opposite sides of the opening.

The present invention has another object in the use of a suture needle-like suture device made of bioabsorbable material and having a coiled configuration in a method of closing an anatomical lumen.

A further object of the present invention is to provide a suture needle-like suture device made of bioabsorbable material that can be locked in tissue to prevent both forward and rearward movement.

An additional object of the present invention is to position a hinge-like joint on a suture needle-like suture device made of bioabsorbable material such that a distal portion of the suture device can be folded at a precise location after penetration of tissue to be juxtaposed with a proximal portion of the suture device to facilitate use of the suture device to produce desired adjustable locking of the distal and proximal portions.

A further object of the present invention is to configure suture needle-like suture devices made of bioabsorbable material to allow a knotting function to be produced similar to tying a knot in a length of suture material during conventional suturing.

The present invention is generally characterized in a suture needle-like suture device made of bioabsorbable material including an elongate body member having a sharp distal end for penetrating tissue and carrying means for locking the suture device in tissue to prevent forward and rearward movement, a suture needle-like suture device made of bioabsorbable material having a hinge-like joint for folding a distal portion at a precise location to be juxtaposed with a proximal portion for adjustable locking, and methods of using the suture devices for joining and approximating tissue, for closing anatomical lumens and for subcuticular suturing.

Some of the advantages of the present invention over the prior art are that surgeons can easily and quickly utilize the suture devices during endoscopic surger to approximate and join tissue without intricate manipulations and to provide suture stitches in a short time since the suture devices have configurations and characteristics to permit manipulation thereof in a manner similar to suture needles, endoscopic surgery can be used for additional procedures due to the reduced time require for suturing coupled with the knotting function provided by the suture devices, and the suture devices can replace conventional suturing with a length of suture material while providing

all of the advantages thereof desired by surgeons.

Other objects and advantages of the present invention will become apparent from the following description of the preferred embodiments taken in conjunction with the accompanying drawings.

DRWDESC:
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a side view of a suture device according to the present invention.

FIG. 1A is a side view of a modification of the suture device of FIG. 1.

FIG. 1B and 1C are broken views of the body member of the suture device of FIG. 1A.

FIGS. 1D and 1E are broken views of the body member of the suture device of FIG. 1.

FIGS. 2, 3 and 3A are side views showing use of the suture device of FIG. 1.

FIG. 4 is a perspective view of another embodiment of a suture device according to the present invention.

FIG. 5 is a perspective view of the suture device of FIG. 4 in a bent configuration.

FIG. 6 is a side view showing use of the suture device of FIG. 4.

FIG. 7 is a side view of a further embodiment of a suture device according to the present invention.

FIGS. 8 and 9 are side views showing use of the suture device of FIG. 7.

FIG. 10 is a side view of another embodiment of a suture device according to the present invention.

FIGS. 10A, 10B and 10C are side views of modifications of the suture device of FIG. 10.

FIG. 11 is an end view of the suture device of FIG. 10.

FIG. 12 is a perspective view showing use of the suture device of FIG. 10.

FIG. 13 is a perspective view showing another use of the suture device of FIG. 10.

FIG. 14 is a perspective view showing another use of the suture device of FIG. 1.

FIG. 15 is a side view of an additional embodiment of a suture device according to the present invention.

FIG. 16 is a side view showing use of the suture device of FIG. 15.

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DETDESC:

DESCRIPTION OF THE PREFERRED EMBODIMENTS

A suture needle-like suture device 20 according to the present invention is illustrated in FIG. 1 and includes an elongate, curved body member 22 having a sharp distal end 24 for penetrating tissue in a manner similar to a suture needle and a bulbous enlarged proximal end 26, the elongate, curved body member 22, having a round shape in cross-section and gradually tapering from proximal end 26 to sharp distal end 24. Angled, whisker-like filaments 28 extend from the body member 22 rearwardly toward proximal end 26 and are positioned around the body member and along the length thereof. The suture device 20 is made of bioabsorbable material and is intended to remain in the tissue to be absorbed therein.

The use of suture device 20 is illustrated in FIGS. 2 and 3 wherein a section of tissue 30 is to be joined to a section of tissue 32. The tissue can be of any configuration from any anatomical part or organ of the body; however, the suture device 20 is particularly useful for various anastomosis or approximating procedures such as vascular anastomosis, bowel anastomosis, closure of anatomical or non-anatomical structures, tuboplasty and skin closure. Due to the smoothly angled orientation of the whisker-like filaments 28, the suture device can penetrate through the tissue in only the forward direction and cannot be moved rearwardly. The sharp distal end 24 is moved to penetrate through tissue section 30 at a position spaced from the end of the tissue section in a manner similar to movement of a suture needle and is thereafter moved to penetrate through tissue section 32 at a position spaced from the end of tissue section 32. The suture device is manipulated with a conventional needle holder in a manner similar to a suture needle and can be easily utilized during endoscopic surgery; and, once the suture device has been positioned as illustrated in FIG. 2, the distal end is grasped and pulled thereby approximating the ends of the tissue sections 30 and 32 as illustrated in FIG. 3, it being noted that the enlarged bulbous proximal end 26 prevents the suture device from pulling through tissue section 30 since the proximal end has a dimension in at least one direction transverse to the body member greater than the transverse dimension of the body member. Once the suture device is in the position illustrated in FIG. 3 with the ends of the tissue sections approximated, the portion of the suture device protruding from tissue section 32 is severed as shown at line 34 leaving the suture device in the tissue. The suture device will remain in position since the angled, whisker-like filaments will not allow the suture device to move rearwardly and the enlarged bulbous proximal end 26 will not allow the suture device to move forwardly. Additionally, by using a shearing cutting device to sever the protruding distal portion of the suture device, the cut end can be expanded to form a flange 35 to further prevent rearward movement of the suture device. A number of suture devices 20 may be required to provide a complete suturing procedure; and, for anastomosis or tuboplasty, as many as four, five or six suture devices may be used dependent upon the size of the tubular structure and the thickness of the wall thereof. The suture device will be absorbed in the tissue after joining and healing of the ends of the tissue sections.

By providing body member 22 with an arcuately and smoothly curving configuration, the suture device 20 can be made of a rigid bioabsorbable material in that pulling the suture device through tissue section 32 causes the suture device to essentially pivot about the proximal end 26 to move tissue

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section 32 to abut tissue section 32. It will be appreciated, however, that suture device 20 can have other configurations and can be made of bioabsorbable materials of varying flexibility or rigidity for use with particular anatomical tissues. For example, suture device 20 can be straight, or rectilinear, as shown in FIG. 1A at 20a, and made of flexible bioabsorbable material to allow the body member 22 to bend as it is drawn through tissue section 32 to approximate the edges of the tissue sections. The proximal end 26 can have any desired configuration to prevent forward movement of the suture device once the suture device has passed through the initial tissue section; for example, the enlarged proximal end could have a flat, nail head-type shape, as shown at 26a in FIG. 1A, or the proximal end could have angled, whisker-like filaments extending forwardly therefrom toward the sharp distal end. The body member can have a uniform diameter therealong with a tapered sharp distal end and can have various cross-sectional configurations and be either solid or hollow. The whisker-like filaments are preferred to provide the function of permitting only forward movement of the suture device through the tissue, or, in other words, preventing reverse movement of the suture device; however, the body member can carry other means of permitting only forward movement such as protrusions of various configurations. By providing the whisker-like filaments along the length of the body member, the suture device 20 provides a knotting function similar to tying a knot in a length of suture material. That is, compression and approximation of the tissue sections can be variably controlled in accordance with the tension applied to the suture device as it is pulled through the tissue by grasping the distal end 24.

The suture device 20a has rearwardly angled protrusions 28a having a truncated conical configuration to permit only forward movement of the suture device, in place of whisker-like filaments 28, the protrusions being shown in FIG. 1B with a solid body member 22a and in FIG. 1C with a hollow body member 22b. When the body member is hollow, the interior lumen can be filled with various pharmacological agents by constructing the proximal end to be detachable, such as by screw threads or a friction fit, and microholes 29 extend radially through the body member to communicate with the lumen and provide passages for the pharmacological agents to leach out into the suture site. As previously noted, the use of whisker-like or hair-like filaments to permit only forward movement of the suture device is preferred in that, as shown in FIGS. 1D and 1E, the filaments lay against body member 22 as the suture device is moved forwardly to penetrate tissue producing minimal obstruction to smooth movement. However, any tendency for the suture device to move rearwardly causes the filaments to protrude, as shown in FIG. 1, to lock the suture device in the tissue. The body member 22 in FIG. 1D is solid while the body member in FIG. 1E is hollow to allow the interior lumen to be filled with a pharmacological agent for leaching into the suture site.

Another embodiment of a suture device according to the present invention is illustrated in FIG. 4. The suture needle-like suture device 36 is integrally formed of bioabsorbable material and includes a proximal portion 38 having an opening 40 therein defining a bottom edge 42 tapering from a small width at the proximal end to be progressively wider. The body of the proximal portion 38 is relatively thick and terminates at a transversely extending recess 44 which forms a hinge-like joint defining a precise bending point from which extends a distal portion 46 tapering to a sharp, suture needle-like point 48 at the distal end of the suture device. A plurality of tapered barbs 50 extend along the distal portion 46 and, as illustrated, have truncated, tetrahedral, pyramidal

shapes while other shapes could be provided as will be understood from the following discussion of the engagement of the barbs with the bottom edge 42 of the opening 40 in the proximal portion 38. For example, whisker-like filaments can protrude from the distal portion for engaging the proximal portion The recess 44 allows the suture device 36 to be bent or folded about the transverse axis thereof, as illustrated in FIGS. 5 and 6, such that the proximal portion 38 and the distal portion 46 can be juxtaposed. The proximal portion 38 has a concave curved configuration and the distal portion 46 has a similar curved configuration such that, when the suture device 36 is bent of folded on itself at recess 44, the opposing ends of the suture device extend in opposite directions.

In use, the sharp point 48 is moved to penetrate section of tissue 52 and 54 to be sutured to approximate the sections of tissue until recess 44 is positioned adjacent the tissue to limit further movement of the suture device, it being noted that the enlarged size of the proximal portion limits penetration in the tissue. The distal portion 46 is then folded in a hinge-like manner about the recess 44, and the sharp distal end 48 is passed through the opening 42 in the proximal portion such that the suture device 36 now has the configuration illustrated in FIG. 5. The proximal and distal portions of the suture device are now forced towards one another such that the sharp distal end 48 passes through the opening 42 to protrude from the bottom as shown in FIG. 6. The distal end 48 can be pulled to adjustably tighten the suture device to provide a knotting function similar to tying a knot in a length of suture material with the barbs 50 engaging the bottom edge 42 of the opening 40 to lock the distal portion in place. The protruding portion of the distal end of the suture device can be severed as shown at line 56. The suture device 36 will thus hold the tissue in approximated position until the tissue is joined after which the suture device 36 will be absorbed in the body.

A modification of the suture device of FIG. 4 is illustrated in FIG. 7 and similar reference numbers with an "a" added are used to identify similar parts. The suture device 36a is made of flexible bioabsorbable material and includes a proximal portion 38a having a proximal end 58 around which is mounted a ring or ring-like member 60 having an opening 42a therethrough with a conical or tapered inner surface defining a locking edge 42a. A transversely extending recess 44a defines a hinge-like joint at the end of the proximal portion 38a, and a distal portion 46a extends from recess 44a and tapers to a sharp, suture needle-like, distal end 48a. Barbs 50a protrude from distal portion 46a angled in a direction away from distal end 48a while a plurality of similar barbs 62 protrude from proximal portion 38a in a direction toward distal end 48a such that the barbs 50a and 62 are angled toward each other prior to use of the suture device, as shown in FIG. 7, but are angled in the same direction when the suture device is bent or folded about recess 44a. The inner surfaces of proximal portion 38a and distal portion 46a are smooth or longitudinally ribbed or grooved to abut and/or lock one another when the suture device is bent at recess 44a.

In use, the sharp distal end 48a is moved to penetrate sections of tissue 52 and 54 to be sutured to approximate the sections of tissue, and the distal portion 46a is pulled through the tissue to position recess 44a adjacent the tissue as shown in FIG. 8. The distal portion is then folded in a hinge-like manner about the recess 44a such that the proximal and distal portions are juxtaposed with the sharp distal end 48a received in the opening 42a in ring 60. The ring 60 is then moved toward the joint (to the left looking at FIGS. 8 and 9), it being appreciated that the inner surface of opening 42a tapers away from

the joint such that the ring can move in only a direction toward the joint. As best shown in FIG. 9, the ring is moved in a manner similar to a knot during conventional suturing with a length of suture material until the ring is positioned as desired; and, once the ring has been properly positioned, the protruding proximal and distal portions are severed as indicated at 56a.

Suture devices 36 and 36a can have various configurations and sizes dependent upon the specific tissue to be sutured, it being important that the suture devices have a well defined bending or folding joint such that the distal portion can be folded in a hinge-like manner after penetration of the tissue to be juxtaposed along the proximal portion and engaged or interlocked with the proximal portion in an adjustable manner to provide a knotting function similar to tying knots with a length of suture material. While the distal portion is adjustably locked in an opening carried by the proximal portion in suture devices 36 and 36a, other adjustable locking means could be used as long as operation thereof can be simply effected to facilitate use. By providing a precise bending position, use of the suture devices by the surgeon is facilitated and standardized allowing the surgeon to simply reproduce the knotting function on a plurality of stitches. Preferably, the suture devices are made of bioabsorbable materials having a hardness and rigidity increasing from the joint toward the proximal and distal ends, and the ring 60 is made of rigid bioabsorbable material.

Another embodiment of a suture needle-like suture device 62 according to the present invention is illustrated in FIG. 10 and includes an elongate body member 64 terminating at a sharp distal end 66 for penetrating tissue in a manner similar to a suture needle and at a bulbous enlarged proximal end 68, the elongate body member having a spiral configuration with the coils disposed in a single plane and having a round shape in cross-section. Angled, whisker-like filaments 70 extend from the body member rearwardly toward proximal end 26 and are positioned around the body member and along the length thereof such that the suture device 62 can pass through tissue in only a forward direction. The suture device is made of flexible, resilient bioabsorbable material such that the suture device contracts after insertion in tissue to be sutured attempting to return to its pre-suturing shape; and, accordingly, the suture device is particularly effective for closing anatomical lumens and subcuticular suturing. The spiral or coiled configuration can also circle about a central axis in curves of conical form, as shown in FIGS. 10 and 10D, or cylindrical form, as shown in FIG. 10B, dependent upon the particular use of the suture device; and, as noted above with respect to suture device 20, the proximal end can have any desired configuration, the cross-section of the body member can vary and the body member can carry other means of permitting only forward movement of the suture device. Additionally, the proximal end 68 can be transposed with the sharp distal end 66 such that the coils become smaller as they approach the distal end. The suture devices shown in FIGS. 10A, 10B and 10C have expanded pre-suturing states, and the coils in FIG. 10A have the same diameter while the diameter of the coils in FIG. 10B increase as they approach the distal end and the diameter of the coils in FIG. 10C decrease as they approach the distal end. Parts of the suture devices 62a, 62b and 62c of FIGS. 10A, 10B and 10C, respectively, are given reference number the same as similar parts of suture device 62 with "a", "b", or "c" added, and the following description of use pertains to suture devices 62, 62a, 62b and 62c.

One use of suture device 62 is shown in FIG. 12 wherein an anatomical lumen

72 in tissue is closed by penetrating the surrounding tissue with the sharp distal end 66 and rotating or screwing the suture device into the tissue until proximal end 68 abuts the tissue. The suture device will be locked in place since forward movement is prevented by proximal end 68 and rearward movement is prevented by the whisker-like filaments 70, and the spiral configuration will close the lumen.

Use of the suture device 62 for subcuticular suturing is shown in FIG. 13 wherein the tissue to be sutured is skin having an outer layer 74 formed of the epidermis and the germinal epithelium and a subcutaneous layer of fat 76 primarily formed of collagen. By penetrating the subcutaneous layer 76 only, and not the outer layer 74, with a series of suture devices 62, a wound or opening in the skin can be closed to facilitate healing and minimize scar tissue. The sharp distal end 66 of the suture device is moved to penetrate the subcutaneous layer 74 where the first stitch is to be taken, and the suture device is rotated to cause the suture device to advance into the subcutaneous layer until the enlarged proximal end 68 engages the tissue at which point the suture device will be locked in place with the two sides of the wound held in close engagement for healing while the suture device is absorbed in the tissue. Thus, suture device 62 can be simply manipulated by a surgeon to close a wound by subcutaneously suturing in a time efficient manner.

FIG. 14 illustrates use of suture device 20 of FIG. 1 for subcutaneous suturing, a series of the suture devices 20 being used in a manner similar to that described above with respect to suture device 62 with the exception that only a single bite of tissue is taken with each suture device 20 as compared with the multiple bites taken with each suture device 62. The number of coils in the suture device determines the number of bites taken thereby; and, thus, it will be appreciated that the number of coils can vary as desired, suture device 20 providing one bite while suture device 62 provides five bites or stitches.

A modification of the hinge-like foldable suture devices 36 and 36a of FIGS. 4 and 7, respectively, is illustrated in FIG. 15 wherein similar parts are given similar reference numbers with a "b" added. The suture device 36b of FIG. 15 is integrally formed of bioabsorbable material and includes a proximal portion 38b having an opening 40b therein, the proximal portion 38b terminating at a transversely extending recess 44b forming a hinge-like joint defining a precise bending point from which extends a distal portion 46b tapering to a sharp, suture needle-like point 48b at the distal end of the suture device. The opening 40b is formed of a tapering recess becoming gradually deeper and wider as it approaches the hinge-like joint. The width of the recess 40b is slightly less than the corresponding width of the distal portion 46b of the suture device when the suture device is folded to juxtapose the proximal and distal portions. The distal portion 46b gradually tapers to sharp distal point 48b and is faceted. Use of the suture device 36b is illustrated in FIG. 16 for suturing tissue 52, for example to occlude a tubular body part or organ. The tissue is penetrated with the sharp distal portion 46b and then folded at recess 44b to juxtapose the distal and proximal portions as shown. The distal portion 44b can then be depressed into the recess opening 40b in an adjustable manner corresponding to the tissue being sutured, the plastic nature of the bioabsorbable material holding the distal portion within the proximal portion.

Various bioabsorbable or biodegradable materials can be used to make the suture devices of the present invention with the composition determined by the

rigidity or flexibility required. Generally, the bioabsorbable materials are thermoplastic polymers, such as absorbable polymers and copolymers of polydioxanne, lactide, glycolide and the like. Polyglycolic acid is disclosed in U.S. Pat. Nos. *3,463,158*; *3,739,773* and *3,772,420*. Suitable polylactic acids are disclosed in U.S. Pat. No. *3,636,956*. Examples of absorbable polyesters are shown in U.S. Pat. Nos. *3,225,766* and *3,883,901*. Absorbable cellulose glycolic acid ethers are shown in U.S. Pat. No. *2,764,159*. Examples of suitable esters of alpha-cyanoacrylic acid are found in U.S. Pat. Nos. *3,527,841*, *3,564,078* and *3,759,264*.

From the above, it will be appreciated that the suture devices according to the present invention have configurations to allow the suture devices to be handled or manipulated by surgeons in a manner similar to conventional suture needles. That is, the surgeon will grasp the proximal end of the suture device, for example with a needle holder, and move the suture needle to penetrate the tissue. The suture devices can be placed in the tissue in a manner to control and adjust the tension on the suture device o the compression of the tissue to produce a knotting function in an efficacious manner easily accomplished by the surgeon such that suturing and knotting can be quickly performed during endoscopic surgery.

Inasmuch as the present invention is subject to various modification and changes in detail, the above description of a preferred embodiment is intended to be exemplary only and not limiting.

CLAIMS: I claim:

[*1] 1. A needle-like suture device for joining bodily tissue comprising

an elongate body member integrally, unitarily made of bioabsorbable material having a sharp distal end for penetrating tissue and a proximal end;

means carried on said proximal end for abutting the tissue and preventing movement of said proximal end forwardly through the tissue; and

means carried on said body member at least at a position adjacent said means carried on said proximal end for moving forwardly through the tissue with said body member and for engaging the tissue to prevent movement of said body member rearwardly through the tissue when said means carried on said proximal end is in abutting relation with the tissue.

[*2] 2. A suture device as recited in claim 1 wherein said means carried on said proximal end includes an enlarged end having a dimension in at least one direction transverse to said body member greater than the transverse dimension of said body member.

[*3] 3. A suture device as recited in claim 2 wherein said enlarged end has a bulbous configuration.

[*4] 4. A suture device as recited in claim 3 wherein said means carried on said body member includes protrusion means extending rearwardly from said body member permitting only forward movement of said body member through the tissue.

[*5] 5. A suture device as recited in claim 1 wherein said means carried on

said body member includes protrusion means extending rearwardly from said body member permitting only forward movement of said body member through the tissue.

[*6] 6. A suture device as recited in claim 5 wherein said protrusion means are whisker-like filaments.

[*7] 7. A needle-like suture device for joining bodily tissue comprising

an elongate body member made of bioabsorbable material having a sharp distal end for penetrating tissue and a proximal end;

means carried on said proximal end for preventing movement of said proximal end forwardly through the tissue; and

a plurality of whisker-like filament means carried on said body member and extending rearwardly from said body member for moving forwardly through the tissue with said body member and for engaging the tissue to prevent movement of said body member rearwardly through the tissue.

[*8] 8. A suture device as recited in claim 7 wherein said whisker-like filament means are disposed along substantially the entire length of said body member.

[*9] 9. A suture device as recited in claim 8 wherein said body member has a curved configuration such that continuous forward movement of said body member causes bodily tissue sections to be approximated.

[*10] 10. A suture device as recited in claim 8 wherein said body member has a coiled configuration.

[*11] 11. A suture device as recited in claim 10 wherein said coiled configuration is a spiral formed of coils having the same diameter.

[*12] 12. A suture device as recited in claim 10 wherein said coiled configuration is a spiral formed of coils having an increasing diameter as they approach said sharp distal end.

[*13] 13. A suture device as recited in claim 10 wherein said coiled configuration is a spiral formed of coils having a decreasing diameter as they approach said sharp distal end.

[*14] 14. A suture device as recited in claim 10 wherein said coiled configuration is a spiral formed of coils disposed in a single plane.

[*15] 15. A needle-like suture device for joining bodily tissue comprising

an elongate body member made of bioabsorbable material having a sharp distal end for penetrating tissue and a proximal end, said body member having a continuously curving configuration between said distal end and said proximal end for pulling tissue together as said body member passes through the tissue;

means carried on said proximal end for preventing movement of said proximal end forwardly through the tissue; and

means carried on said body member for moving forwardly through the tissue with said body member and for engaging the tissue to prevent movement of said body member rearwardly through the tissue.

[*16] 16. A suture device as recited in claim 15 wherein said body member has a coiled configuration.

[*17] 17. A suture device as recited in claim 16 wherein said coiled configuration is a spiral formed of coils having the same diameter.

[*18] 18. A suture device as recited in claim 16 wherein said coiled configuration is a spiral formed of coils having an increasing diameter as they approach such sharp distal end.

[*19] 19. A suture device as recited in claim 16 wherein said coiled configuration is a spiral formed of coils having a decreasing diameter as they approach such sharp distal end.

[*20] 20. A suture device as recited in claim 16 wherein said coiled configuration is a spiral formed of coils disposed in a single plane.

[*21] 21. A needle-like suture device for joining bodily tissue comprising

an elongate body member made of bioabsorbable material having a sharp distal end for penetrating tissue and a proximal end, said body member having a lumen formed therein for holding a pharmacological agent and holes therein communicating with said lumen to allow said pharmacological agent to leach into the suture site;

means carried on said proximal end for preventing movement of said proximal end forwardly through the tissue; and

means carried on said body member for engaging the tissue and preventing movement of said body member rearwardly through the tissue.